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# STUDIES OF PERIPHERAL BLOOD VASCULAR BEDS IN THE BULBAR CONJUNCTIVA OF MAN*

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An earlier, more general report from this laboratory (1) upon peripheral blood vascular beds included a group of observations upon the bulbar conjunctiva of man. The observations indicated that the vascular patterns "may exhibit endless variety, at times to the point of apparent 'randomness', and suggesting no definite plan of organization interpretable in terms of structural units of the most ill-defined sort." On the other hand, Chambers and Zweifach (2)—on the basis of extensive studies of the frog's mesentery, the rat's mesoappendix and the dog's omentum—had arrived at a concept of the peripheral vascular bed as a composite of structural and functional units, each unit having as its basic architectural feature a central, capillary-like, arterio-venous, preferential or "thoroughfare" channel, of which the true capillaries are side-branches. Lee and Holze (3, 4) interpreted their findings in terms of the full applicability of this concept to the human bulbar conjunctiva. As noted elsewhere (1), "The area of disagreement is wide, and there is an obvious need for further detailed studies in this region." An acute awareness of this need led us to re-investigate the problem, with markedly improved equipment, in an attempt to resolve apparent discrepancies in the findings of the two groups of investigators.

For the present studies, a brief preliminary report of which has appeared in this journal (5), we have employed a Zeiss Opton Stereo-Microscope, provided with 10× oculars and 2× supplemental lens, in a range of from 6 to 80 magnifications; and a Mikrark (wolfram-zirconium) Illuminator with 100 watt bulb (Boone Instrument Co., New York), and provided with heat-absorbing and Wratten green (Eastman B, no. 58) filters. Occasional use has likewise been made of yellow (Eastman G, no. 15) and "theater light blue" (Corning #4308, polished, 4 mm. thick) filters, but we have found the green filter preferable for most purposes. Subjects have been studied in the recumbent position, with angular incident illumination. The use of a pad of foam rubber under the sub-

*We are deeply indebted to Miss Alice E. Fruehan, Mr. Charles C. J. Carpenter, Jr., Mr. Donald P. Hahn and Mr. Philip R. B. McMaster for their intelligent cooperation and patience in serving as subjects for these studies; and to Miss Mary E. McCarthy for the painstaking care with which she completed the drawings.

ject's head has proved extremely helpful, particularly at the higher magnifications, more or less delicate pressure upon the head serving as a fine focusing adjustment. Under these conditions, we have been able to achieve far better visualization of certain features of the conjunctival vascular beds than in previous studies (1), which were clearly inadequate in a number of important respects.

## OBSERVATIONS

At this stage of the problem, our primary objectives have been two in number, the architecture of the conjunctival beds and the character and behavior of their constituent vessels. There seemed to be no question that the most fruitful approach to both of these objectives would be intimate acquaintance with selected, though limited, beds in which we could certify, with a high degree of assurance, that the vascular pattern was complete; and it is along these lines that we have concentrated our efforts during the present studies. We knew from previous experience that this would not be an easy task, even with the best equipment, since automatic, uncontrollable movements of the eyeball make sharp visualization progressively more difficult as the magnification is increased. Also, the phenomena of vasomotion, capillary intermittence, etc. impose the added requirement of repeated check and recheck of all features of a given bed over a suitably long period of time.

Our principal findings, with respect to architecture of the peripheral vascular patterns, are illustrated in the accompanying series of figures, which are freehand drawings accomplished at magnifications up to 80×. All subjects were normotensive and, so far as is known, in excellent health; all but one (Fig. 8) were in the 22–24 year age group. Except for those illustrated in figures 9 and 10, all patterns were located entirely in the most superficial layer of the conjunctiva, and were not overlain by any vessels from adjacent fields. With one exception they were oriented in the eye as reproduced; the pattern shown in figure 1 was oriented at an angle of c. 35 degrees to the vertical, and has been rotated clockwise to the vertical for purposes of reproduction.

Our recent experience confirms the endless variety of the vascular patterns, and the lack of any recognizable structural and functional unit in the sense of Chambers and Zweifach (2). However, interposed between obviously arterial and obviously venous channels, we have repeatedly encountered—in addition to presumptive "true capillaries"—vessels of appreciably larger than capillary size, and apparently of the nature of arterio-venous communications, of quite different functional significance than the capillaries themselves. These arterio-venous communications, which will be discussed further below, are of such frequent occurrence as to constitute a characteristic feature of the peripheral vascular beds. Apparently unequivocal examples of this type of vessel have

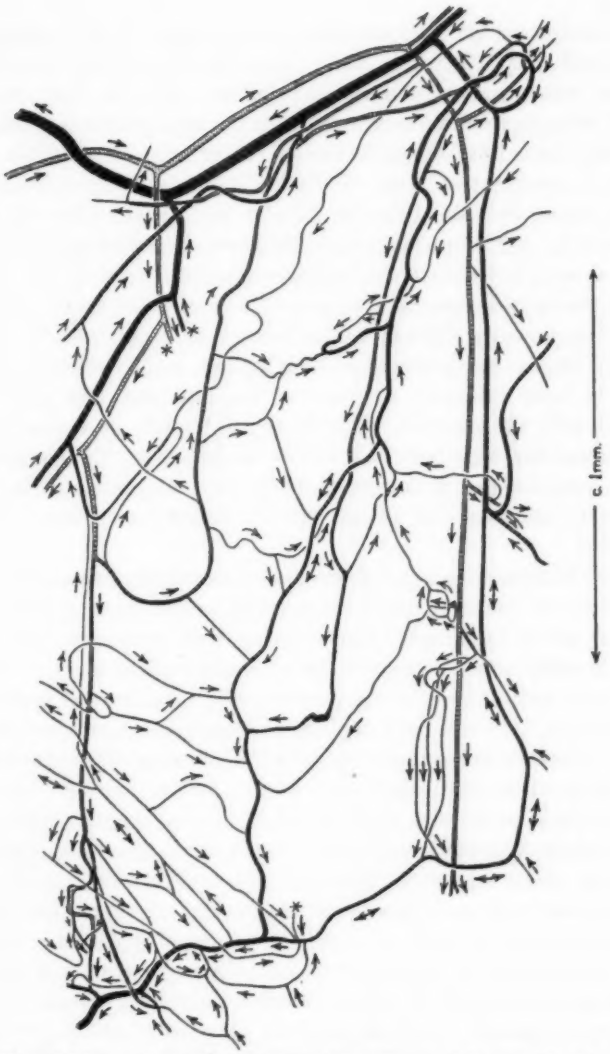


FIG. 1. Superficial vascular pattern, temporal quadrant, right eye, about mid-way between corneoscleral limbus (to right) and outer canthus, and between superior (above) and inferior conjunctival fornices. Male subject, 24 years. c. 60×.

been indicated in the figures, for which the following conventions have been adopted:

All obviously arterial and arteriolar channels have been drawn with double contours and stippled; and the same is true of arterio-venous anastomoses (in the usual sense) and communications (of the type described above), these channels being represented as arterial up to the most proximal points of entry of blood which has already passed through one or more presumptive capillaries. Possible or presumptive "true capillaries" have been represented by single-thickness lines; and all obviously venular and venous channels have been represented by solid lines of greater thickness. The varying thickness of the arterial, venous, arterio-arterial, arterio-venous and veno-venous channels, as shown in the figures, gives an approximate idea of their relative calibers in the original vascular beds. The convention of single-thickness lines for "capillaries" inevitably suppresses variations in their caliber, and in addition makes them appear—in some instances, at least—of disproportionately small caliber as compared with the channels of other types. Vessels consistently exhibiting unidirectional flow have been indicated by single arrows, those exhibiting more or less frequent reversal of flow by double arrows. An asterisk (*) has been used to designate vessels which ascend from or descend to a lower level of the conjunctiva.

The field illustrated in figure 1 was chosen essentially at random, the choice being limited to the companion arterial and venous loops (upper right-hand corner) as useful landmarks. The drawing was completed and thoroughly checked in many study periods in the course of three months. A considerable variety is at once evident in the pattern, which has several features of particular interest. Only the most striking arterio-venous communications are so indicated; however, it seemed more than likely that additional vessels were of this character rather than capillary in nature. In the lower left-hand corner of the figure, the continuation of the principal arterial channel, with an obvious fusiform enlargement in its course, has been shown as arterial up to the entrance of the first small tributary. However, this enlargement usually exhibited sluggish flow at best, and was more or less static much of the time. Some of the presumptive capillaries were, to a variable degree, of appreciably larger caliber at their venous than at their arterial ends; the most striking of these is illustrated above and to right of center. Another interesting feature is the curious skein of three parallel vessels in the lower right-hand corner. Still another is the fusiform enlargement in the course of one of the smaller veins (below and to right of center). The pattern includes two veno-venous anastomoses of moderate caliber, one bounding the field to the right and below, the other just to right of center; both exhibited reversal of flow on numerous occasions.

The field illustrated in figure 2 was selected for analysis and drawing follow-

FIG. 2. Superficial vascular pattern, temporal quadrant, right eye, about mid-way between limbus (to right) and outer canthus, and between superior (above) and inferior conjunctival fornices. Female subject, 24 years. c. 60×.

ing the chance observation of the rather prominent veno-venous anastomosis located below top center. All details were checked repeatedly over a period of three and one-half months. As in figure 1, the pattern exhibits a considerable variety, and the fields are quite dissimilar. The presenting feature of this pattern is the presence of the companion arterio-arterial and veno-venous anastomoses, both of which exhibited frequent reversal of flow. An additional striking feature is the rather large number of apparently unequivocal arterio-venous communications.

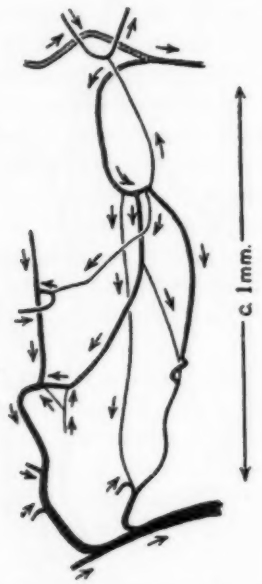


FIG. 3. Superficial vascular pattern, temporal quadrant, right eye, about mid-way between limbus (to right) and outer canthus, and between superior (above) and inferior conjunctival fornices. Female subject, 24 years. c. 60×.

The more limited fields illustrated in figures 3 to 7 were selected for study either because, in a preliminary survey of the region, they appeared to be as simple and delicate as any which were encountered (Figs. 3, 4 and 6); because of the presence of a rather prominent arterio-venous communication (Fig. 5); or essentially at random (Fig. 7). The drawings were completed in multiple study periods in the course of 10, 13, 10, 21 and 31 days respectively. The patterns are largely self-explanatory, and require but brief comment. Attention should be drawn to the unusual and constant fusiform enlargement of the artery in the lower right-hand corner of figure 4. In figure 5, the principal

artery (above and to right) emerges from a somewhat deeper level, just nasal to the limbus, and courses in an essentially straight line to the first branching point included in the figure. The curious complex of arterio-venous communications (near left margin) is also noteworthy.

The presenting feature of the pattern illustrated in figure 6 is the large number of apparently unequivocal arterio-venous communications. Additional striking features are the arterio-arterial anastomosis (center), of small caliber

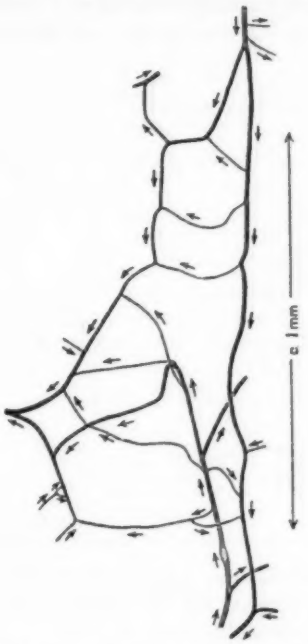


FIG. 4. Superficial vascular pattern, temporal quadrant, right eye, about mid-way between limbus (to right) and outer canthus, and somewhat closer to the inferior (below) than to the superior conjunctival fornix. Male subject, 22 years. c. 60×.

and exhibiting reversal of flow; and the veno-venous anastomoses (top), one of which exhibited reversal of flow. The venous loop and stirrup formation (upper left-hand corner), with its associated veno-venous anastomosis (extending to right), showed different flow patterns at different times; and these were frequently accompanied by appreciable (even rather marked) changes in caliber of individual portions of the formation. The two portions which exhibited the most pronounced variations in caliber were the right arm of the stirrup and the large veno-venous anastomosis. The pattern in figure 7 is

characterized by a high degree of complexity, the large majority of the smaller vessels being presumptive "true capillaries," some of which could be visualized only at isolated intervals. There were in this subject an unusual "looseness" of the superficial layer of the conjunctiva, and a tendency to "cloudiness" which at times was quite distressing, so that the drawing was completed only with great difficulty. Attention is drawn to the arterio-venous communications near the upper and right-hand margins of the figure.

Figure 8 is a revised and corrected drawing of a pattern previously analyzed, with equipment inferior to that now in use, and published in an earlier volume

FIG. 5. Superficial vascular pattern, nasal quadrant, left eye, a short distance from limbus (to right), and about mid-way between superior (above) and inferior conjunctival fornices. Female subject, 24 years. c. 60×.

of this journal (1, p. 65). The two analyses were accomplished approximately one year apart. In terms of our more recent experience, a number of the smaller vessels previously interpreted as presumptive "true capillaries" would qualify as arterio-venous communications of the type described above.

The arterio-venous anastomosis illustrated in figure 9 was sufficiently bold to attract attention in a preliminary survey of the region, and is fairly representative of such anastomoses as encountered at times below the surface of the conjunctiva. The pattern as drawn is "stripped," with no attempt to trace further connections of its branches and tributaries, and is overlain by the capillaries, etc. of the most superficial vascular beds. As it approaches the point of entry of the first tributary (at bottom), the arterial channel exhibits a rather marked increase in caliber.

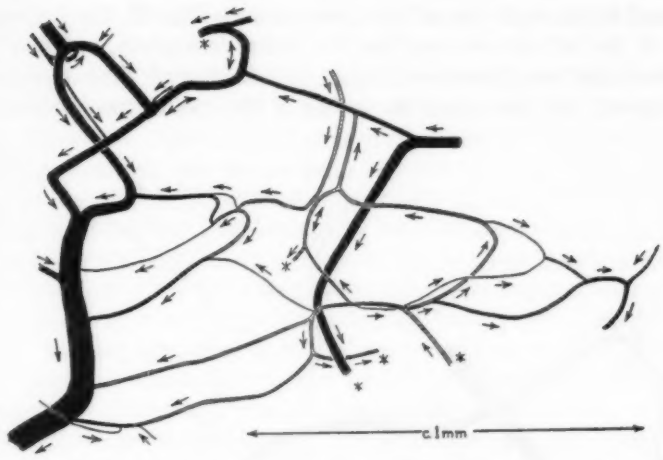


FIG. 6. Superficial vascular pattern, temporal quadrant, right eye, about one-third the distance between limbus (to right) and outer canthus, and somewhat closer to the inferior (below) than to the superior conjunctival fornix. Male subject, 23 years. c. 60×.

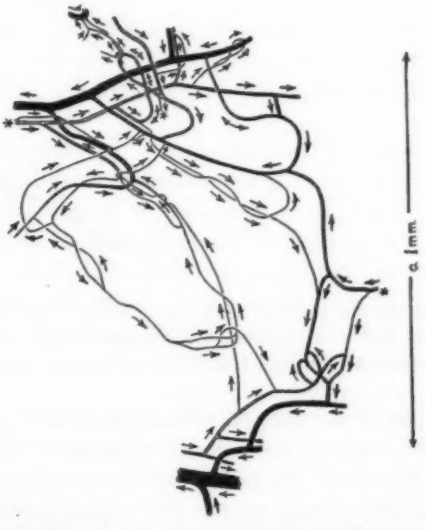


FIG. 7. Superficial vascular pattern, temporal quadrant, right eye, about mid-way between limbus (to right) and outer canthus, and between superior (above) and inferior conjunctival fornices. Female subject, 24 years. c. 60×.

Associated arterio-arterial and veno-venous anastomoses having been encountered in the right eye of the same subject (Fig. 2), the corresponding region of the left eye was searched for similar formations, and revealed the much bolder pattern illustrated in figure 10. Like figure 9, the pattern as drawn is "stripped," and lies below the surface of the conjunctiva. Because of the

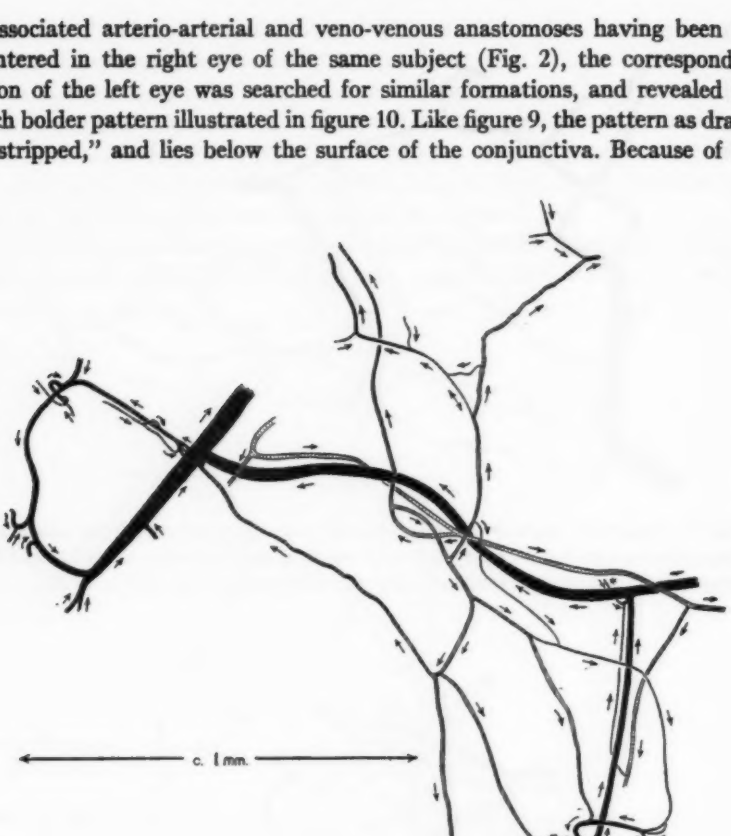


FIG. 8. Superficial vascular pattern, temporal quadrant, left eye, about mid-way between limbus (to left) and outer canthus, and somewhat closer to the superior (above) than to the inferior conjunctival fornix. Male subject, 47 years. c. 60×.

relative depth of the structures and difficulties of sharp visualization, additional small arterial branches and venous tributaries could easily have been missed. The field affords a most interesting demonstration of reversal in the direction of blood flow in both arterial and venous channels of considerable size, and the basis therefor in terms of arterio-arterial and veno-venous anastomoses. It seems likely that reversal of flow may occur in additional portions of the vascular complex; however, such were not detected in repeated observa-

tions over a period of two and one-half months. The pattern has been extended in all directions to include vessels which consistently showed unidirectional flow.

Obviously, in any study of the architecture of peripheral blood vascular beds, particularly in so far as it might reveal the presence of more or less repetitive features of organization (i.e., structural and functional units), it is of primary importance that the patterns selected for analysis should be as complete as possible. In the patterns illustrated in figures 1–8, we have made every effort to insure such completeness by repeated observations at intervals over periods of many days or, in the case of figures 1 and 2, several months. Capillary intermittence is of frequent occurrence in the conjunctiva, and some capillaries transmit blood only very occasionally. The problem is further complicated by the fact that, even under the best conditions, we have been consistently unable to visualize the actual walls of the capillaries, or to detect their presence when they are "empty" (i.e., free of erythrocytes).

It would, of course, be tremendously helpful if there were some ready means to produce peripheral vasodilatation under such conditions that all constituent vessels of a given bed were actively transmitting blood at the same time. However, our efforts to achieve this result by various means (including drugs) have thus far been unsuccessful. Under the circumstances, it seemed wisest to proceed on the assumption that even occasionally active capillaries would eventually reveal their presence if a given bed were observed at more or less frequent intervals over a sufficiently long period of time. Although there will always be an element of doubt, we believe that this procedure has been on the whole highly successful, and that the patterns as illustrated are essentially, if not entirely, complete.

With our present equipment, visualization of blood flow in all superficial vessels, irrespective of type or caliber, presents no appreciable difficulty. Variably active "vasomotion"—in the sense of variations in speed of flow, alterations in caliber of individual vessels, and alternation between activity and inactivity (i.e., intermittence) of capillaries—can be detected regularly and with ease. In obviously arterial channels, the more usual picture is one of essentially continuous flow at good speed, sufficiently rapid so that individual erythrocytes cannot be recognized. However, the pictures can vary over a wide range. At times, the flow alternates irregularly between more and less rapid rates, but remains continuous. At other times, a rapid flow is reduced more or less gradually or abruptly, and comes almost to a halt (or on occasion stops altogether) for a brief interval; then surges forward again, rather quickly attaining a variably rapid rate. This type of surging flow may be continued over periods of considerable length, and may be quite striking. On occasion, with a forward surge of blood, the smaller arterial channels appear definitely to increase appreciably in caliber.

The small arterio-venous communications, referred to above as a characteristic feature of conjunctival vascular beds, require further comment. In the earlier phases of the work, it appeared that these communications could probably be distinguished from presumptive "true capillaries" by three criteria: 1. caliber—usually larger than that of capillaries; 2. participation in vasomotion, with surging flow; 3. continuous flow, though at variable speed, when capillaries showed intermittence and inactivity. However, as the work progressed, and we became more and more intimately acquainted with selected vessels of this type, it became obvious that one, two or all three of these criteria could break down on occasion. Although in no sense rigid, the criteria appear to be generally applicable, and there seems to be no doubt that such a class of vessels exists in goodly numbers in the bulbar conjunctiva of man. At times, these arterio-venous communications appear to participate actively in vasomotion; at other times their changes in caliber, etc. appear to be purely passive; and it is frequently impossible to make a decision in this regard, the problem being further complicated by the automatic movements of the eyeball. During the changes in caliber of these channels, we have not as yet observed saccular dilatations (2) in their proximal portions or elsewhere in their course. Neither have we been able to detect the presence of "precapillary sphincters" (2, 6–8) at the points of emergence of presumptive "true capillaries" from such channels.

Blood flow in the veins is usually continuous, at not exceeding a moderate rate of speed compared with that in the arteries. However, here again the pictures are variable. More or less irregular alternation between slower and more rapid rates of flow is frequently noted. On occasion, when the rate is slow or very slow, the small veins exhibit what can best be described as a "granular" type of flow. At times the flow is observed to cease altogether, after which the contained erythrocytes may or may not shuttle back and forth for an appreciable period before flow is resumed in a forward direction. During these studies we have observed no instance of

FIG. 9. A rather prominent arterio-venous anastomosis lying below the superficial layer of the conjunctiva, temporal quadrant, right eye, about mid-way between limbus (to right) and outer canthus, and between superior (above) and inferior conjunctival fornices. Male subject, 22 years. c. 60×.

FIG. 10. A vascular pattern lying below the superficial layer of the conjunctiva, and including arterio-arterial and veno-venous anastomoses, temporal quadrant, left eye, about mid-way between the limbus (to left) and outer canthus, and between superior (above) and inferior conjunctival fornices. Female subject, 24 years. c. 40×.

agglutination of erythrocytes, "sludging" in the sense of Knisely *et al.* (9, 10), or adhesion of leukocytes to the endothelium of veins or other vessels.

## DISCUSSION

As indicated above, these studies have abundantly confirmed our earlier conclusion (1) that Chambers and Zweifach's (2) concept of structural and functional units—built around preferential, capillary-like, "thoroughfare" channels—does not apply to the peripheral blood vascular beds in the bulbar conjunctiva of man. In this regard, our disagreement with Lee and Holze's (3, 4) interpretation of their findings is as wide as before. On the other hand, in confirmation of Lee and Holze's observations, these studies have revealed—so repetitively as to be a characteristic feature of the conjunctival beds—the presence of numerous, small, arterio-venous communications, apparently subserving functions significantly different from those of the presumptive "true capillaries," and of such capacity as to permit delivery of rather large amounts of blood into the veins when the capillaries themselves are closed. The more exact characterization of these communications must await further study. However, from their caliber and behavior they would appear to be in large measure similar to the preferential, "thoroughfare" channels of Chambers and Zweifach; and equivalent to at least some of the "A-V thoroughfares" of Lee and Holze and of the "through and through channels" of Lack *et al.* (11).

A consideration of the extensive literature upon biomicroscopy of the conjunctival vessels, in health and disease, as well as upon peripheral blood vascular beds elsewhere in the body, would be beyond the scope of this report. Many of the more important references have been included in an earlier publication in this journal (1).

## SUMMARY

As a supplement to earlier studies, a description is given of various aspects of peripheral blood vascular beds in the bulbar conjunctiva of man. Particular emphasis has been placed upon thorough analysis and illustration of selected vascular patterns in normotensive young adults. The patterns exhibit endless variety, and the lack of any recognizable structural and functional unit in the sense of Chambers and Zweifach. Small arterio-venous communications are of such frequent occurrence as to constitute a characteristic feature of the conjunctival beds. Arterio-venous anastomoses of larger size are likewise encountered, as are arterio-arterial and veno-venous anastomoses. The latter two types of channel afford an adequate basis for the frequently observed reversal in the direction of blood flow in arterial and venous channels of considerable size. Under normal conditions, the conjunctival vessels exhibit varying degrees of spontaneous vasomotion, which may be quite striking.

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# THE EFFECT OF CORTISONE UPON REACTIONS OF RABBITS TO BACTERIAL ENDOTOXINS WITH PARTICULAR REFERENCE TO ACQUIRED RESISTANCE*

IVAN L. BENNETT, JR., AND PAUL B. BEESON

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Received for publication September 14, 1953

The injection of endotoxins, pyrogens or toxic somatic antigens derived from Gram-negative bacteria is followed in man and many animals by fever and transient leukopenia (1). Many of these substances are potent in eliciting the Shwartzman reaction and they are also capable of causing death in appropriate dosage. Because of the similarity of these reactions to the manifestations of active infection, as well as the probability that in certain diseases, endotoxins play a role in the production of symptoms (2), the modification of reactions to endotoxins by adrenocorticotrophic hormone (ACTH) or cortisone has been studied by several investigators.

Kass and Finland (3) found that the febrile response of human beings and of rabbits to intravenously administered typhoid vaccine was attenuated by prior treatment with ACTH. Recant, Ott, and Fischel (4), using a pyrogenic pneumococcal vaccine and a pyrogen from *Pseudomonas*, described an antipyretic action of cortisone in rabbits. Although these workers made no detailed attempt to quantitate their results, they stated that it seemed likely that the degree of antipyretic effect was related to the dose of cortisone administered. Duffy and Morgan (5) demonstrated clearly that the febrile response of rabbits to purified *Shigella dysenteriae* (*Shiga*) endotoxin may be either suppressed or aggravated by ACTH or cortisone depending upon the amount of hormone used and the timing of its administration.

Shwartzman, Schnierson, and Soffer (6) reported inhibition of the Shwartzman reaction in rabbits by ACTH or cortisone administered as a single dose 2 hours before the intravenous "provocative" injection of bacterial toxin. Thomas and Good (7, 8, 9), however, in an extensive series of studies, have found that administration of ACTH or cortisone for 3–4 days before testing not only fails to suppress the Shwartzman reaction but actually results in a striking increase in the susceptibility of rabbits to this type of injury, local or generalized, and to the lethal effect of bacterial endotoxins. Prior treatment of rabbits with a single injection of various colloidal materials such as Thorotrast, trypan blue, etc. results in a similar increase in susceptibility to endotoxins. On the basis of the known effect of colloids in "blockading" the fixed macrophages of the reticulo-endothelial system (RES), Thomas has postulated that the aggravation of toxicity of bacterial products by cortisone may also involve some interference with a protective function of the RES. This suggestion is in accord with Beeson's finding that both Thorotrast and trypan blue effectively abolish acquired tolerance to the febrile response to endotoxins (10) or to the dermal Shwartzman

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reaction (11). Animals or human beings given daily injections of bacterial endotoxin rapidly develop resistance or tolerance to its pyrogenic effect, responding with less and less fever until a minimal response is reached (12, 13, 14). If the local Shwartzman reaction is elicited repeatedly in rabbits at short intervals, a similar state of non-reactivity appears (11). The production of skin-hemorrhage is not necessary for the development of resistance to the reaction; repeated injection of endotoxin by several routes is effective in producing it (15, 16). Tolerance to fever and resistance to the production of skin lesions of the Shwartzman type are similar in several respects (16). Both are non-specific in that resistance acquired by exposure to the endotoxin of one bacterial species is operative against products of other species. Neither is related to specific antibody formation or is transferable by serum. Both are transient, disappearing rapidly when frequent injections are stopped; lastly, both are abolished promptly by injection of Thorotrast or trypan blue.

In view of the suggestion (9) that the increased susceptibility of *normal* animals to the Shwartzman reaction after cortisone may involve a mechanism similar to that of Thorotrast, it seemed worthwhile to compare the effect of these materials in animals *resistant* to fever and the Shwartzman reaction. It might be expected that cortisone would abolish acquired resistance to these effects of endotoxins in the same way that Thorotrast does. The present report describes investigations showing that this is not the case. Certain observations upon the time-dose relationship between ACTH and cortisone and pyrogen fever in rabbits as well as the failure of these hormones to exert an influence upon the leukocyte changes produced by endotoxins are also included.

## MATERIALS AND METHODS

Male New Zealand white rabbits weighing 2–3 Kilos were used throughout the study.

Bacterial pyrogens and endotoxins employed were: P-35 polysaccharide from *Serratia marcescens* (obtained from Dr. M. J. Shear), a culture filtrate of *S. marcescens*, typhoid vaccine containing one billion organisms/ml. (obtained from the Georgia State Department of Health), and Piromen, a *Pseudomonas* concentrate (kindly supplied by Baxter Laboratories as a suspension containing 50 μg./ml.).

ACTH was purchased commercially. Cortisone acetate was kindly supplied by Merck and Company as a suspension containing 25 mg./ml.

In experiments on fever, animals were placed in metal stalls secured by a loose-fitting collar and rectal temperatures were taken at intervals of 30 minutes using resistance coils which remained in the rectum throughout the test period and an automatic recording device (the Foxboro Rabbit Scanner and Fever Recorder). Rabbits were allowed appropriate periods of acclimatization to the stalls before use and adequate numbers of baseline recordings were made before injection of pyrogen into the marginal ear vein. To facilitate comparison of results, the areas under fever curves of individual rabbits were measured with a planimeter (Keuffel and Esser #4236M) and the vernier reading of this instrument was taken as the "fever index," an indication of both height and duration of fever (13).

The dermal Shwartzman reaction was elicited with P-35 polysaccharide in a dose of 0.05 mg. in 0.5 ml. of 0.85% NaCl solution intracutaneously and 0.1 mg. in 1.0 ml. intravenously 22 hours later. The skin dose of *S. marcescens* filtrate was 0.5 ml. of 1:5 dilution and the intravenous 1.0 ml. of 1:20 dilution. When multiple skin injections were given, the first was made in the right upper quadrant of the abdomen, the second in the left upper

quadrant, the third on the right just behind the first, etc., alternating sides of the abdomen and moving the sites posteriorly. Hair was removed with electric clippers immediately prior to injection. Each lesion was recorded by tracing on x-ray film with colored pencils immediately before the intravenous provocative injection, 4 hours later, and 24 hours later. These tracings were later transcribed to permanent records. The criterion for classifying lesions as positive was the presence of confluent skin hemorrhage.

All glassware, needles, etc., were sterilized in hot air ovens at 170°C. for 2 hours to destroy bacterial pyrogen contaminants; saline solutions and distilled water were tested at regular intervals by intravenous injection in rabbits and were always pyrogen-free.

## EXPERIMENTAL RESULTS

### *Effect of Varying Doses of ACTH or Cortisone upon the Febrile Response of Normal Rabbits to a Single Injection of Endotoxin*

Groups of normal rabbits were given intramuscular injections of ACTH or cortisone by various schedules and their temperature responses were recorded after a single injection of bacterial pyrogen. The following schedules for administration of the hormones were employed:

*Group A*—2.5 mg. ACTH twice daily followed by 2.5 mg. on the second day immediately before pyrogen injection.

*Group B*—5 mg. ACTH twice daily for 2 days and 5 mg. on the third day immediately before pyrogen injection.

*Group C*—10 mg. ACTH twice daily for 7 days and 10 mg. on the eighth day immediately before pyrogen injection.

*Group D*—2.5 mg. cortisone twice daily followed by 2.5 mg. on the second day immediately before pyrogen injection.

*Group E*—2.5 mg. cortisone twice daily for 2 days and 5 mg. on the third day immediately before pyrogen injection.

*Group F*—5 mg. cortisone twice daily for 7 days and 5 mg. on the eighth day immediately before pyrogen injection.

Schedules A, B, D, and E were chosen to correspond with the dosages employed by Duffy and Morgan (5) in their studies with Shigella endotoxin. Five or 6 animals from each group were tested by injection of 1 ml. of 1:200 typhoid vaccine, 1 ml. of 1:8 typhoid vaccine or 2 ml. of Piromen (100 μg.). Normal control animals were also inoculated with each of these pyrogens and fever indices were determined for all animals.

The results of these experiments are shown in Figs. 1–3. There were differences in the responses of the various groups to the same pyrogen and responses in each group varied with the pyrogenic stimulus used. Animals in groups A and C showed increased fevers with typhoid vaccine and group B showed a lessened response. With Piromen, groups A and B varied only slightly from the controls but group C animals had higher fevers. Animals in groups D, E and F showed decreased febrile responses after all three dosages of pyrogen with the single exception of group F animals tested with Piromen which showed increased fevers as compared to normal controls given this same pyrogen.

The results of these experiments demonstrate clearly that there is great

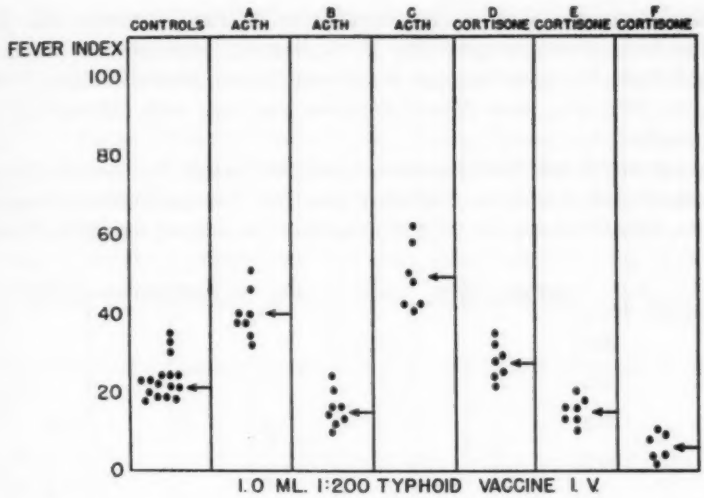


FIG. 1. Fevers in rabbits given ACTH or cortisone in varying amounts and tested with 1.0 ml. of 1:200 typhoid vaccine intravenously. See text for details of hormone dosage. Each point is the fever index of one animal; the arrows indicate the mean fever index for each group.

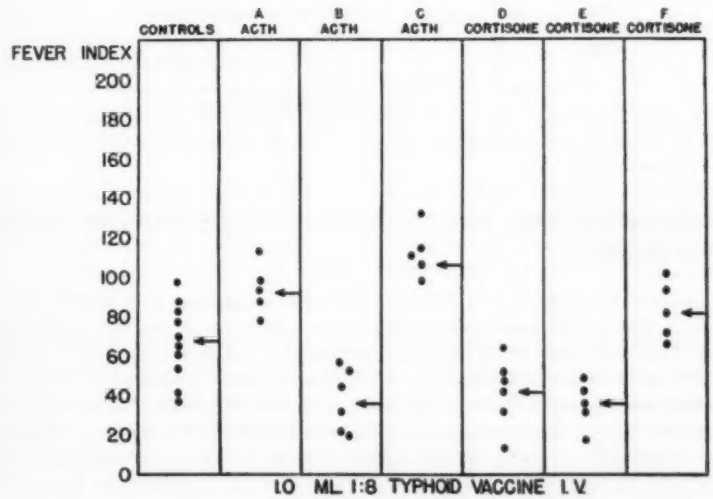


FIG. 2. Fevers in groups of rabbits given ACTH or cortisone and tested with 1 ml. of 1:8 typhoid vaccine intravenously.

variation in the modification of pyrogen fever by these hormones. The febrile response to a given pyrogen may be suppressed, increased or remain unchanged depending upon hormone dosage and time of administration. Furthermore, the effect of a given dose of hormone may vary with different amounts of endotoxin.

*Effect of ACTH and Cortisone upon Leukocyte Changes Produced by Pyrogens.* —To test the effect of these hormones upon the leukopenic effect of bacterial pyrogen, animals were given ACTH or cortisone in varying dosage and changes

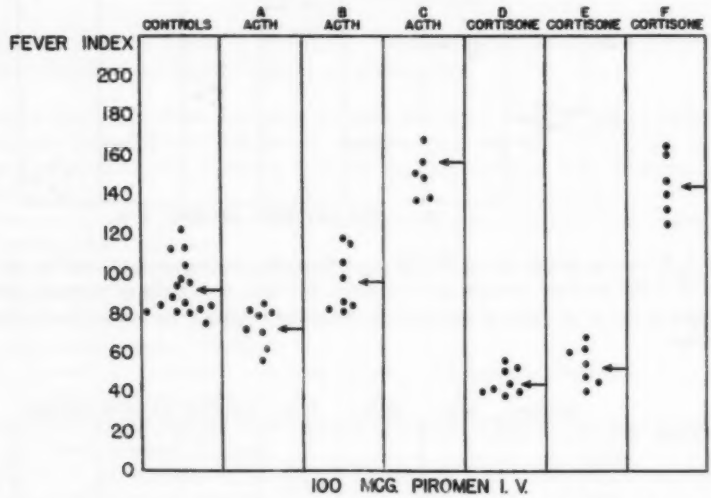


FIG. 3. Fevers in groups of rabbits given ACTH or cortisone and tested with 100 μg. Piromen intravenously.

in circulating leukocytes were determined by serial counts after injection of bacterial pyrogen.

Groups of 6 rabbits were given ACTH or cortisone by schedules A–F as in the preceding experiment. Ten normal animals served as controls. Leukocyte counts were made on blood obtained from small cuts in the ear. After preliminary leukocyte counts, each animal received 100 μg. of Piromen intravenously and leukocyte counts were made at 5, 15, 30 and 60 minutes and at hourly intervals thereafter until the sixth hour. All animals, controls and hormone-treated, developed prompt leukopenia followed in 4–5 hours by leukocytosis. Despite considerable variation in fever in rabbits given ACTH or cortisone in the dosage used (see Fig. 3), there was no difference in the behaviour of the leukocytes. As can be seen in Table I, the extent of leukopenia was entirely comparable in all groups.

This experiment indicates that the variation in fevers of animals given the hormones is not dependent upon any alteration in hematologic responses.

There is no evidence that the leukocyte changes after pyrogen administration are related to the production of fever. Indeed, animals made profoundly leukopenic by nitrogen mustard respond to pyrogen administration with brisk fevers (17).

*Effect of Larger Doses of Cortisone for Varying Periods before Pyrogen Administration.*—To study further the time-dose relationship between cortisone treatment and pyrogen-induced fever in rabbits, larger doses of this hormone were administered to rabbits for varying lengths of time and febrile responses to a single injection of pyrogen were recorded. A daily dose of 25 mg. of cortisone was used because this is the amount found by Thomas and Good (7) to enhance susceptibility to the Shwartzman reaction if administered daily for 3 or 4 days.

TABLE I

*Failure of ACTH or Cortisone to Modify Leukopenic Effect of Bacterial Pyrogen in Rabbits*

| RABBITS | TOTAL LEUKOCYTE COUNTS‡ | | |
|---|---|---|---|
| | Preliminary | Lowest | % Decrease |
| Controls (10)* | 8,092 ± 1,126 | 2,542 ± 423 | 68.7 |
| A† (6) | 7,600 ± 1,914 | 2,587 ± 516 | 70.7 |
| B (6) | 11,575 ± 2,423 | 2,800 ± 724 | 74.0 |
| C (6) | 8,425 ± 1,843 | 2,750 ± 930 | 67.4 |
| D (6) | 10,850 ± 2,071 | 3,212 ± 614 | 69.4 |
| E (6) | 13,700 ± 2,784 | 3,687 ± 1,041 | 63.1 |
| F (6) | 10,187 ± 2,246 | 3,082 ± 993 | 69.8 |

* Numbers in parentheses refer to animals included in each group.

† See text for details of hormone dosage.

‡ All figures refer to mean ± standard error.

Groups of 6–10 rabbits were treated with single injections of 25 mg. of cortisone daily for periods of 1 to 10 days and were then given 1 ml. of 1:8 typhoid vaccine intravenously and their fevers measured. In this way, the daily dose of cortisone and the dose of pyrogen were kept constant and variations in response could be attributed to the length of the pretreatment period.

Fig. 4 shows the individual and mean febrile responses of all animals in this experiment including 15 normal controls given no hormone. Animals given cortisone from 1 to 6 days showed a progressive diminution of fever index as compared to controls. However, beginning on the seventh day of hormone administration, fevers gradually increased and exceeded control levels after 9 and 10 days. The indices for the ninth and tenth day groups averaged 76 and 74 respectively as compared to the control mean of 61.

The results of this study make it evident that the length of time that cortisone dosage is continued is important in determining the extent of the febrile re-

sponse to endotoxin. With a daily dose of 25 mg. of cortisone, the antipyretic effect which is evident after the first day abruptly gives way after 7 days to accentuation of the febrile responses.

*Effect of Termination of Cortisone Treatment upon the Febrile Response to Endotoxin.*—To test the possibility that the loss of antipyretic effect with continued cortisone administration after the seventh day might be due to an inhibitory effect of large doses of hormone upon the activity of the animal's own adrenals, this deficiency being incompletely compensated by cortisone alone, rabbits were given pyrogen at varying intervals after cessation of

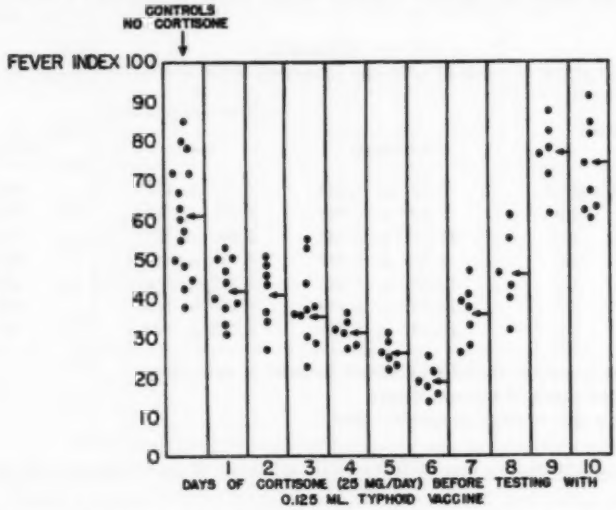


FIG. 4. Fevers of rabbits given 25 mg. of cortisone daily for periods of 1–10 days and then tested by intravenous injection of 1 ml. of 1:8 typhoid vaccine. Note the progressive antipyretic effect of this dosage of cortisone until the seventh day. Fevers on days 9 and 10 exceeded control levels.

hormone administration. It was reasoned that if a sudden accentuation of the febrile reaction to pyrogen became demonstrable during the withdrawal period, this might indicate that endogenous adrenal depression played a role.

Normal rabbits were given 25 mg. of cortisone daily for 7 days. At this time, hormone administration was stopped and beginning on the 8th day, groups of animals were given 1 ml. of 1:8 typhoid vaccine intravenously daily and their febrile responses recorded. This was continued through the 12th day so that observations were made on groups of rabbits on each of the first 5 days after withdrawal of cortisone. The results of fever measurements in these five groups are shown in Fig. 5 and compared with normal controls. There was no sudden "overshoot" of fever during the period when cortisone was stopped. The mean fever index increased in steplike fashion until on the fourth and fifth days it approximated the control level.

The exact mechanism involved in the change of reactivity of rabbits on cortisone to pyrogens after 1 week is not explained by the results of this experiment but it seems clear that it cannot be attributed to adrenal suppression or to sudden failure of cortisone to be effective in the animals. The increased fevers in rabbits given cortisone for 9 or 10 days are not due to a simple loss of antipyretic action of the hormone through a tolerance to its effects but apparently represent some true enhancing effect of cortisone itself.

*Effect of Cortisone upon the Development of Tolerance to Bacterial Pyrogens.*—The variation in cortisone's effect upon the febrile response of rabbits to single

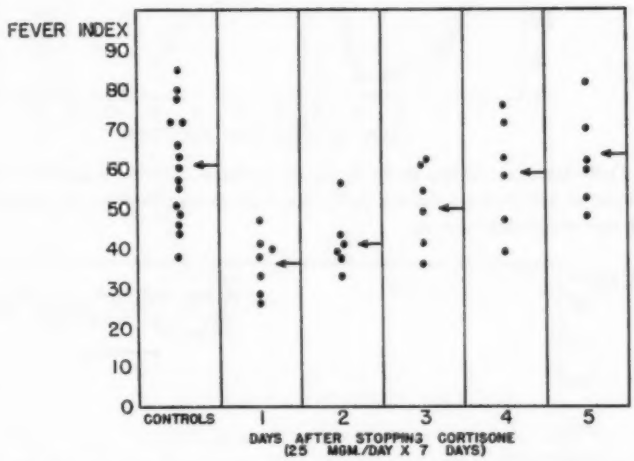


FIG. 5. Fevers of groups of rabbits given 1 ml. of 1:8 typhoid vaccine at various intervals after completing a course of 25 mg. of cortisone daily for seven days. Note the gradual return to control levels after cessation of hormone treatment as contrasted with the accentuation of febrile responses in animals continued on cortisone in Fig. 4.

injections of endotoxin led to an evaluation of its influence upon the response of animals to repeated injections.

Two schedules of hormone and pyrogen administration were used. Six rabbits were given 25 mg. of cortisone daily for 3 days and daily injections of 1 ml. of 1:8 typhoid vaccine were begun on the fourth day, hormone injections also being continued. Cortisone was given intramuscularly each morning immediately before pyrogen administration. The febrile response of each animal was recorded daily after typhoid vaccine injection. Six additional rabbits were begun on daily injections of 25 mg. of cortisone and 1 ml. of 1:8 typhoid vaccine, the period of pretreatment with the hormone being omitted.

Fig. 6 illustrates the course of daily fevers in the group of animals pretreated with cortisone for 3 days before regular injections of pyrogen were begun. Fever indices fell progressively during the first four days of pyrogen treatment,

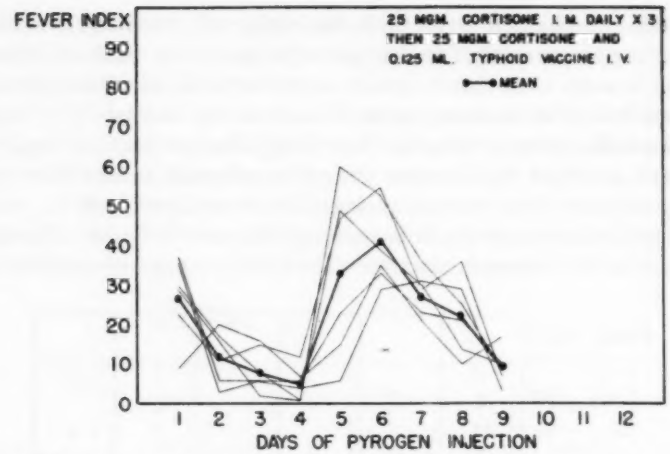


FIG. 6. Daily fevers in rabbits given 25 mg. of cortisone daily for 3 days and then cortisone and 1 ml. of 1:8 typhoid vaccine daily. Note the abrupt increase in fevers beginning on the fifth day of pyrogen injection.

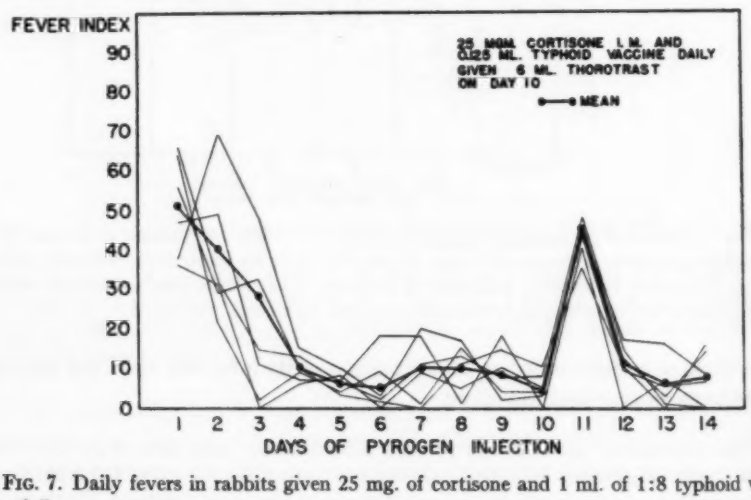


FIG. 7. Daily fevers in rabbits given 25 mg. of cortisone and 1 ml. of 1:8 typhoid vaccine daily.

but beginning on the fifth and sixth days, there was an abrupt rise in fevers in all animals followed by progressive decline to low levels by the ninth day. The accentuation of febrile responses reached its peak on the sixth day of pyrogen injection (the ninth day of cortisone treatment).

In contrast, the animals given cortisone and typhoid vaccine together showed

progressive decrease in fevers; no sudden rise in febrile responses appeared although injections were continued for 10 days (Fig. 7). On the tenth day, each animal was given 6.0 ml. of Thorotrast intravenously and there was an abrupt increase in fevers on the following day. With continued pyrogen administration on days 12–14, febrile responses again fell to tolerant levels. This effect of Thorotrast corresponds to what is seen in normal animals made resistant to pyrogens.

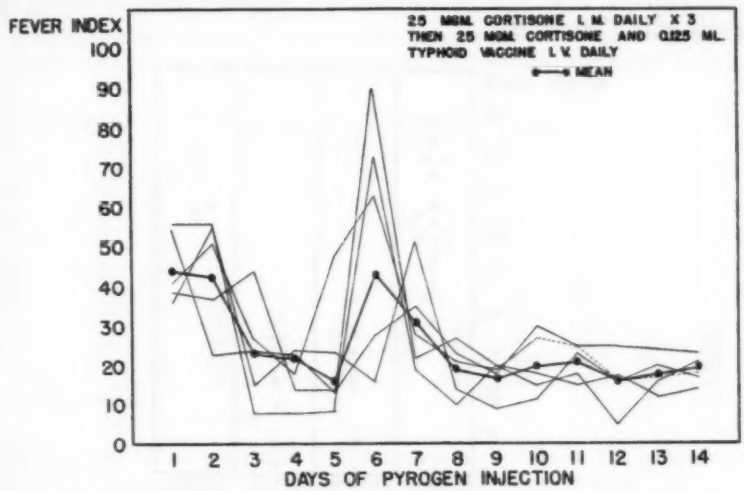


FIG. 8. Daily fevers in rabbits given 25 mg. of cortisone daily for 3 days and then cortisone and 1 ml. of 1:8 typhoid vaccine daily. Note that after a brief period of accentuation of fevers from day 5 to 7, responses returned to low levels.

Another group of five animals received 25 mg. of cortisone daily for 3 days and beginning on the fourth day, typhoid vaccine injections were added and fevers recorded. As can be seen in Fig. 8, after an initial decrease in fevers, there was again an abrupt accentuation of febrile responses between the fifth and eighth days of pyrogen treatment (eighth to eleventh days of cortisone) but with continued injections, fevers returned to low levels and remained there until the fourteenth day when the experiment was terminated.

These experiments indicate that the continued administration of cortisone does not interfere with the ultimate development of resistance in rabbits to the pyrogenic effect of endotoxin. If cortisone and pyrogen are begun at the same time, tolerance appears quickly and persists and this tolerance is abolished promptly by Thorotrast injection. If cortisone is begun 3 days before pyrogen injections, an initial decrease in febrile responses is interrupted abruptly after about 7 days of hormone injection by a sharp upward swing in fevers. This striking accentuation of fever, however, again gives way to minimal responses

and resistance persists for at least 14 days. This difference in results depending upon whether cortisone is given first or is begun at the same time that pyrogen injections are instituted is reminiscent of the accentuation of febrile responses to a single injection of pyrogen in animals given cortisone for more than 7 days (Fig. 4). It is to be emphasized that these findings can be applied only to these specific dosages of cortisone and of pyrogen.

*Effect of Thorotrast and Cortisone upon Established Tolerance to Fever.*—The effect of cortisone in animals with established resistance to pyrogen fever was compared with Thorotrast.

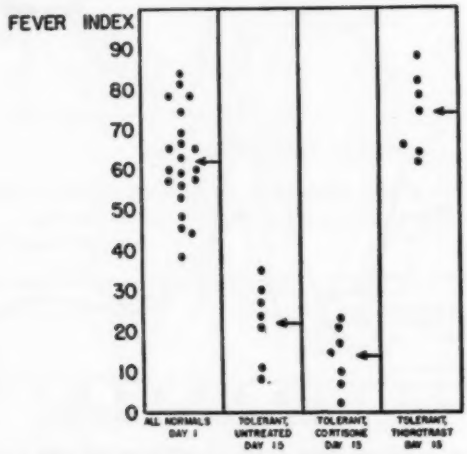


FIG. 9. Fevers of rabbits made tolerant to 1 ml. of 1:8 typhoid vaccine by daily injections for 14 days and then retested as controls, after 25 mg. of cortisone daily for 3 days, or after a single intravenous injection of 6.0 ml. of Thorotrast. Note the failure of cortisone to elevate fevers while Thorotrast resulted in loss of resistance.

Twenty-one normal rabbits were given 1 ml. of 1:8 typhoid vaccine intravenously and their temperature responses were recorded. Their fever indices averaged 62. Daily injections of typhoid vaccine were continued for 14 days and on the fifteenth day, after various types of pretreatment, typhoid vaccine was again given and fevers were recorded. Seven rabbits received daily pyrogen injections only and served as controls. Seven were given 6.0 ml. of Thorotrast intravenously on day 14, 16 hours before the final test injection of pyrogen, and seven received 25 mg. of cortisone intramuscularly on days 12, 13 and 14. The febrile response of all animals on the fifteenth day is compared with first day fevers in Fig. 9. Controls demonstrated resistance to the pyrogen, their fevers averaging 22; Thorotrast-treated animals all had high fevers (mean 73), indicating abolition of resistance by this colloid; cortisone-treated animals uniformly showed temperature responses lower than the untreated tolerant animals (mean 14).

This striking difference in the effects of cortisone and of Thorotrast in animals tolerant to the pyrogenic effect of bacterial endotoxin suggests that in this

circumstance, at least, Thorotrast and cortisone do not act in the same way in influencing the febrile response to endotoxin. Because of the possible influence of dosage and timing of hormone administration, a second experiment was done in which cortisone's effect was determined after periods of 1 to 7 days in tolerant animals.

Eight normal rabbits were given 1 ml. of 1:8 typhoid vaccine daily for 14 days. All animals became tolerant, the mean fever index falling from 54 on the first day to 22 on the ninth and 19 on the fifteenth. Beginning on the fifteenth day, all animals were given 25 mg. of cortisone daily; pyrogen injections were continued and fevers were measured daily. All animals continued to respond with low fevers (Fig. 10) until the twenty-second day

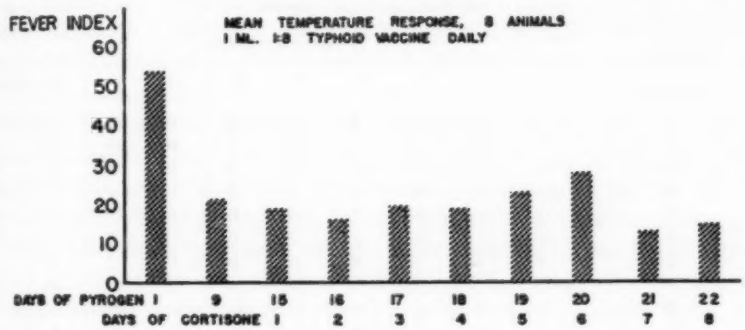


FIG. 10. Mean febrile response in 8 rabbits resistant to 1 ml. of 1:8 typhoid vaccine given 25 mg. of cortisone and 1 ml. of 1:8 typhoid vaccine daily for 8 days.

of pyrogen at which time cortisone had been given for 7 days. The experiment was terminated at this point. Fig. 10 illustrates the mean fevers in these animals before and after hormone treatment.

Under the circumstances of these studies and with the dosage of cortisone and of pyrogen employed, no evidence of interference with established resistance to pyrogen fever by this hormone was demonstrable. In contrast, Thorotrast abolished tolerance promptly.

*Effect of Cortisone upon the Development of Resistance to the Local Shwartzman Reaction.*—Because of the previously mentioned similarities between resistance to fever and the resistance which develops to repeated elicitation of the dermal Shwartzman reaction, the effect of cortisone in rabbits subjected to this reaction on alternate days was observed.

Sixteen rabbits were given intracutaneous preparatory injections of P-35 polysaccharide on the first, third, fifth, etc., days and on even-numbered days, intravenous provocative injections of P-35 were administered. All skin lesions were observed and recorded as described previously. Eight animals also received 25 mg. of cortisone intramuscularly daily beginning on the first day.

The course of events in these two groups of animals was strikingly different. In the eight control rabbits, skin lesions diminished progressively in size until, by the eighth day, all animals had reached a state of non-reactivity and no skin hemorrhage appeared. Animals treated with cortisone, however, continued to show large hemorrhagic skin lesions as long as alternate skin and intravenous doses of endotoxin were administered. These animals rapidly lost weight, became weak and debilitated, and only three survived the experiment which was

TABLE II

*Effect of Cortisone upon the Development of Resistance to the Dermal Shwartzman Reaction Elicited with P-35 Polysaccharide (Shear)*

Appearance of skin lesions

| ANIMALS | DAY OF EXPERIMENT* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 |
| 1 | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | + | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 |
| 7 | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8 | + | + | + | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9† | + | + | + | + | + | + | + | Died | | |
| 10 | + | + | + | + | + | + | + | + | + | + |
| 11 | + | + | + | + | + | Died | | | | |
| 12 | + | + | + | + | Died | | | | | |
| 13 | + | + | + | + | + | + | + | Died | | |
| 14 | + | + | + | + | + | + | + | + | + | + |
| 15 | + | + | + | + | + | + | + | + | + | + |
| 16 | + | + | + | + | + | + | + | + | Died | |

* Lesions were examined 4 and 24 hours after intravenous provocative injections which were given on even-numbered days.

† Animals 9–16 received 25 mg. cortisone intramuscularly each day.

+ = positive Shwartzman reaction.

0 = negative Shwartzman reaction.

terminated after 20 days. Table II shows the effect of cortisone in preventing development of non-reactivity in these animals. Animals which died during the course of this experiment were autopsied; in no case was renal cortical necrosis observed although rabbits given cortisone are susceptible to this lesion (7).

This experiment was repeated on two occasions using *S. marcescens* filtrate in two groups of 24 rabbits, 12 of each group serving as controls and 12 receiving cortisone. In no instance did any animal receiving the hormone develop a state of non-reactivity to the Shwartzman reaction. Normal animals regularly became resistant after the production of 1 to 4 dermal lesions.

These studies indicate that cortisone, in the dosage used, interferes strikingly with the development of resistance to the dermal Shwartzman reaction. This is in sharp contrast to the development of resistance to the pyrogenic effect of endotoxins which is sometimes transiently affected by cortisone but ultimately appears in all animals.

*Effect of Thorotrast and Cortisone upon Established Tolerance to the Shwartzman Reaction.*—The effect of cortisone in animals already resistant to the dermal Shwartzman reaction was studied and compared with Thorotrast injection.

Twenty-four rabbits were subjected to repeated dermal Shwartzman reactions, elicited with *S. marcescens* filtrate, until all had exhibited at least 2 negative reactions. Eight were then given 6.0 ml. of Thorotrast intravenously, eight were begun on daily injections of 25 mg. of cortisone and eight served as controls. Injections of filtrate were continued in all animals.

Table III shows the results of this experiment. Control animals continued to be non-reactive. All animals in the group given Thorotrast showed positive reactions and one rabbit died; with repeated injections of filtrate, however, they again become non-reactive. Animals given cortisone showed large areas of skin hemorrhage repeatedly as long as hormone injections were continued and 2 of this group died. When cortisone administration was stopped after 10 days, the surviving animals immediately became non-reactive again. After two negative reactions, the six surviving rabbits that had received cortisone were given 6.0 ml. of Thorotrast intravenously and on the next day, all responded with hemorrhagic skin lesions; two animals died within 24 hours after the provocative dose of filtrate. This type of experiment was repeated twice with groups of 24 animals and in every instance, rabbits resistant to the Shwartzman reaction reacted with skin hemorrhage repeatedly during administration of cortisone; the non-reactive state returned promptly when injections of hormone were stopped.

On the basis of these results it was concluded that animals with acquired resistance to the dermal Shwartzman reaction can be made reactive by cortisone or by Thorotrast.

The failure of cortisone to duplicate the effect of Thorotrast in eliminating the tolerance to pyrogen fever suggested the possibility that the results with cortisone in the Shwartzman reaction might be due to some local action on skin reactivity rather than a general systemic effect possibly involving the reticuloendothelial cells. An attempt was made to check this possibility by observing the effect of injection of cortisone in the skin of resistant animals.

Six animals were made resistant to the dermal Shwartzman reaction. Three selected skin sites in each animal were then treated as follows. The first was injected with 0.5 ml. of 0.85% NaCl solution at six-hour intervals for 12 hours before preparation with toxin and these injections were continued until the intravenous provocative injection of filtrate

was given. The second and third skin areas were injected at similar intervals with 0.5 ml. of a suspension of cortisone containing 2.0 μg. of hormone or 0.5 ml. of a solution of hydrocortisone containing 2.0 μg. of hormone. The results of this and a similar study using 4 resistant animals were entirely negative. No lesions appeared at any of the prepared sites. The dosage of hormones employed was selected because it approximates the plasma concentration of these substances after intramuscular administration (18).

TABLE III

*The Effect of Cortisone and of Thorotrast upon Established Resistance to the Dermal Shwartzman Reaction Elicited with S. marcescens Filtrate*

| ANIMALS | Appearance of skin lesions: DAY OF EXPERIMENT* | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 |
| 1 | + | + | 0 | 0 | 0 | 0 | 0 | | | | | | | | |
| 2 | + | + | + | + | 0 | 0 | 0 | | | | | | | | |
| 3 | + | 0 | 0 | 0 | 0 | 0 | 0 | | | | | | | | |
| 4 | + | + | 0 | + | 0 | 0 | 0 | | | | | | | | |
| 5 | + | + | + | 0 | 0 | 0 | 0 | | | | | | | | |
| 6 | + | + | 0 | 0 | 0 | 0 | 0 | | | | | | | | |
| 7 | + | + | + | + | 0 | 0 | 0 | | | | | | | | |
| 8 | + | + | + | 0 | 0 | 0 | 0 | | | | | | | | |
| 9 | + | 0 | 0 | 0 | 0 | 0 | T+ | + | 0 | 0 | 0 | | | | |
| 10 | + | + | 0 | 0 | 0 | 0 | T+ | 0 | 0 | 0 | 0 | | | | |
| 11 | + | + | + | + | 0 | 0 | T+ | 0 | 0 | 0 | 0 | | | | |
| 12 | + | + | + | 0 | 0 | 0 | T+ | Died | | | | | | | |
| 13 | + | 0 | 0 | 0 | 0 | 0 | T+ | + | 0 | 0 | 0 | | | | |
| 14 | + | + | + | + | 0 | 0 | T+ | 0 | + | 0 | 0 | | | | |
| 15 | + | + | 0 | 0 | 0 | 0 | T+ | 0 | 0 | 0 | 0 | | | | |
| 16 | + | 0 | 0 | 0 | 0 | 0 | T+ | 0 | 0 | 0 | 0 | | | | |
| 17 | + | + | 0 | 0 | 0 | 0 | C+ | + | + | + | + | 0 | 0 | T+ | 0 |
| 18 | + | + | + | 0 | 0 | 0 | C+ | + | Died | | | | | | |
| 19 | + | + | + | + | 0 | 0 | C+ | + | + | + | + | 0 | 0 | T+ | Died |
| 20 | + | + | + | 0 | 0 | 0 | C+ | + | + | + | + | 0 | 0 | T+ | 0 |
| 21 | + | 0 | 0 | 0 | 0 | 0 | C+ | + | Died | | | | | | |
| 22 | + | + | + | + | 0 | 0 | C+ | + | + | + | + | 0 | 0 | T+ | + |
| 23 | + | + | 0 | 0 | 0 | 0 | C+ | + | + | + | + | 0 | 0 | T+ | 0 |
| 24 | + | + | + | 0 | 0 | 0 | C+ | + | + | + | + | 0 | 0 | T+ | Died |

T—Received 6.0 ml. of Thorotrast i.v. on preceding day.
C—Received 25 mg. cortisone daily, days 13 through 22.
* Skin injection on odd days; intravenous injection on even days.

These results were not unexpected inasmuch as cortisone has been shown to increase susceptibility to the generalized Shwartzman reaction as well as the local lesion (7).

## DISCUSSION

The finding that the febrile response of rabbits to bacterial endotoxins may be suppressed, accentuated or relatively unchanged after administration of

ACTH or cortisone confirms the earlier work of Duffy and Morgan (5). It has been further shown that the effect of a given dose of hormone upon fever may vary with different amounts of pyrogen and that the length of the pretreatment period with hormone influences the response to a fixed dose of endotoxin. With the doses of cortisone and endotoxin employed in this study, an early antipyretic effect of cortisone was replaced after about one week by an increase in susceptibility of animals to the fever-promoting effect of endotoxin. The failure of sudden stoppage of cortisone treatment to result in increased fever is evidence against adrenal suppression as a factor in this accentuation and also rules out a sudden decrease in effectiveness of the hormone as a cause of the changed response after seven days. It is clear from these results that any discussion of the effect of cortisone or ACTH upon pyrogen fever must be based upon specific definition of dose of hormone, time of administration and dose of endotoxin employed as a stimulus.

Cortisone, in doses known to increase susceptibility of rabbits to tissue injury by bacterial endotoxins, interfered transiently with the development of resistance to fever when hormone injections preceded pyrogen administration and not at all when hormone and pyrogen injections were begun simultaneously. The abrupt appearance of increased fevers in animals pretreated with cortisone and given daily injections of pyrogen occurred at about the time that accentuation of febrile responses to single injections of pyrogen was noted, after seven days of hormone therapy. The mechanism of this transient increase in susceptibility to the pyrogenic effect of endotoxin is obscure. Attempts to correlate the changed reactivity of rabbits given cortisone for seven days with other biochemical and metabolic effects of this hormone are being carried out although findings thus far have been unrevealing. Animals already resistant to pyrogens maintained their refractory state for as long as 8 days on large doses of cortisone. Thorotrast, however, regularly abolished fever resistance in normal or cortisone-treated rabbits.

In contrast, cortisone prevented the development of non-reactivity to the dermal Shwartzman reaction, and rabbits already resistant to this type of injury again exhibited large hemorrhagic skin lesions when cortisone injections were begun, in much the same fashion that Shwartzman resistance is eliminated by Thorotrast. These findings in animals *resistant* to the dermal Shwartzman reaction are in accord with the results obtained by Thomas and Good (7) in *normal* rabbits.

The failure of cortisone to interfere with tolerance to the pyrogenic effect of endotoxins might be interpreted as evidence that the basic mechanism of its action differs from that of Thorotrast in increasing susceptibility to bacterial endotoxins. Although the striking similarity between acquired resistance to fever and to the Shwartzman reaction suggests a close relationship, it should

be pointed out that the ability of an animal to react with fever or with dermal hemorrhage is influenced by many factors. For instance, neither the local nor generalized Shwartzman reaction can be elicited in animals made leukopenic by nitrogen mustard or benzene (19, 20) while leukopenic rabbits respond to endotoxin injections with fevers which differ in no way from those of normal animals (17). Heparin, in doses which inhibit coagulation of the blood, protects animals against the Shwartzman reaction (21, 22) but is without effect upon the pyrogenic response (22). It is entirely possible that cortisone has some antipyretic action which masks fever as an evidence of increased susceptibility to endotoxin. The injection of large amounts of endotoxin produces widespread damage to small blood vessels (23) and vascular injury is characteristic of the Shwartzman reaction (22, 24). The febrile response of rabbits to bacterial pyrogens is predominantly a result of decreased heat loss due to peripheral vasoconstriction (25, 26). It is conceivable that cortisone, which has been shown to influence the response of arterioles and venules to various types of noxious stimuli (27) may render blood vessels more susceptible to damage by endotoxin and at the same time interfere with vasoconstriction to such a degree that the febrile response is attenuated. This hormone may also have some central effect upon thermal balance. Experiments designed to test some of these factors in relation to cortisone's influence on fever are now in progress.

## SUMMARY

The influence of ACTH and cortisone upon reactions to bacterial endotoxins (fever, leukopenia, the Shwartzman reaction) has been investigated in rabbits. The febrile response to a single injection of endotoxin may be decreased, increased or unchanged by treatment with these hormones, depending upon dose of pyrogen, dosage of hormone and time of administration. Evidence is presented that the occasionally observed accentuation of fever by cortisone is not the result of endogenous adrenal suppression.

Although acquired resistance to pyrogen fever is abolished by Thorotrast, cortisone does not interfere with this tolerance. Acquired resistance to the dermal Shwartzman reaction, however, is promptly removed by either cortisone or Thorotrast.

Neither ACTH nor cortisone influenced the degree of leukopenia produced by endotoxin injection.

It is pointed out that the difference in the effects obtainable with these hormones in fever necessitates a careful definition of dosage schedules in discussing their antipyretic effect. The difference in the effects of Thorotrast and of cortisone upon tolerance to fever and resistance to the Shwartzman reaction are discussed and it is suggested that a separate antipyretic effect of cortisone may at times mask its accentuation of endotoxin injury in experiments using fever as a criterion.

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# THE ASSOCIATION OF ADULT-TYPE COARCTATION OF THE AORTA WITH ENDOCARDIAL FIBROELASTOSIS IN INFANCY

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"Adult-type" coarctation of the aorta, which has been defined by Abbott (1) as a "more or less abrupt narrowing—of the descending arch in the region of the insertion of the (usually obliterated) ductus arteriosus" is frequently diagnosed during life in childhood. The patient, however, survives to adulthood and dies in the prime of life as a result of one of numerous complications due to hypertension, to bacterial endocarditis, or rupture of the aorta (Gross 7, Reifenstein *et al.* 11). There are only 14 reported cases of autopsies of this type of coarctation in young children or infants. These cases are listed in Table I in order of age, with the author, the blood pressure when recorded, and the stated cause of death as revealed by the autopsy. The condition of the endocardium, when commented upon, is also included.

In 3 of these cases "fibroelastosis" or fibro-elastic sclerosis of the endocardium was described as the cause of death. Weinberg (15) considered the fibroelastosis as the cause of failure, with coarctation an incidental finding; Levine (8), as well as Edmonds and Seelye (4) also stressed the importance of the thickened endocardium as the prime factor in the production of failure and death. Bahn *et al.* (2) noted endocardial sclerosis, morphologically similar to so-called fibroelastosis, in all 3 of their infants dying in heart failure with adult-type coarctation; but they felt that the heart failure was due to lack of development of adequate collateral circulation. They considered the endocardial sclerosis of "secondary nature and a consequence of left ventricular dilatation incident to failure".

Five infants, dying in this hospital, have shown adult-type coarctation of the aorta at autopsy. These cases are reported because of the interesting observation that when death was associated with heart failure, the coarctation was associated with severe endocardial fibroelastosis. In the single case dying of acute pneumonia, there were no signs or symptoms of associated failure and the coarctation was an asymptomatic incidental finding.

## CASE REPORTS

Only the pertinent facts in the histories and autopsies are recorded.

*Case 1:* J. D.—A96663 was admitted for the first time to the Harriet Lane Home 10–3–52 at the age of 4 months. There was a history of respiratory difficulty since birth. Rales, rhonchi and wheezes were heard in the lungs. The heart sounds were of poor quality; gallop rhythm at the apex; no murmurs. EKG showed changes suggestive of left ventricular hy-

pertrophy and myocarditis. X-rays showed diffuse cardiac enlargement. Blood pressure in the arms was 94/54; in the legs 80/?. The impression was that this represented non-specific myocarditis or fibroelastosis. The patient was digitalized and discharged after 2 weeks on maintainence digitalis. The second admission to Harriet Lane was 11–9–52 after a short history of cough, fever, dyspnea and anorexia. Pneumonia was diagnosed. The blood pressure in the arms was now 160/60. As the patient was thought to have digitalis intoxication, digitalis was temporarily stopped, but resumed before discharge. The third and last admission was 12–13–52 after being seen several times in the Out Patient Department with bronchitis. Blood pressure was now 117/70 in the arm. The baby seemed acutely ill with rales and rhonchi over both lung hilums. The heart was grossly enlarged to the left, rate rapid, 150; sounds of poor quality with gallop at apex. No murmurs heard; no venous distension; femoral pulses were good. Liver was down 5 cm. Thought to have bilateral pneumonia. Put on terramycin, digitalis and oxygen, but respiratory difficulty increased and died on second hospital day, at 7 months of age.

TABLE I

*Adult-type Coarctation in Infancy Reported in the Literature*

| AUTHOR | AGE | BLOOD PRESSURE | | STATED CAUSE OF DEATH | CONDITION OF ENDOCARDIUM |
|---|---|---|---|---|---|
| | | Arm | Leg | | |
| 1. Calodney & Carson (3) | 22 days | 160/88 | 0 | Hemorrhagic disease of newborn | Not described |
| 2. Bahn, Edwards, DuShane (2) | 6 weeks | Not reported | | Heart failure | Endocardial sclerosis |
| 3. Bahn, Edwards, DuShane (2) | 7 weeks | Not reported | | Heart failure | Endocardial sclerosis |
| 4. Edmonds & Seelye (4) | 2 mos. | Not reported | | Fibroelastosis | Fibroelastosis |
| 5. Etlinger (5) | 3 mos. | Not reported | | Pneumonia, heart failure | Not described |
| 6. Calodney & Carson (3) | 4 mos. | Not reported | | Pneumonia | Not described |
| 7. Olney & Stephens (9) | 4½ mos. | Not reported | | Heart failure; mitral stenosis | Not described |
| 8. Weinberg & Himmelfarb (15) | 5 mos. | Not reported | | Fibroelastosis | Fibroelastosis |
| 9. Bahn, Edwards, DuShane (2) | 25 wks. | Not reported | | Heart failure | Endocardial sclerosis |
| 10. Sala & Nachamie (12) | 6 mos. | Not reported | | Pneumonia | Not described |
| 11. Wadstein (14) | 7 mos. | Not reported | | Capillary bronchitis | Not described |
| 12. Levine (8) | 10 mos. | Not reported | | Fibroelastosis | Fibroelastosis |
| 13. Stephens & Grimes (13) | 13 mos. | 130/85 | 85/70 | Cardiac arrest during resection coarctation | Not described |
| 14. Olney & Stephens (9) | 14 mos. | Not reported | | Cardiac arrest following resection coarctation | Not described |

Autopsy #24044 was performed 12–13–52 by Dr. Shaka, 3 hours after death. The infant was well developed, weighing 5¼ kg. and measuring 67 cm. in length. The heart was huge, weighing 145 grams (normal weight at 7 months is 34 grams). Although the right ventricle was hypertrophied, it was overshadowed by the tremendous hypertrophy and great dilatation of the left ventricle, which showed diffuse opaque white thickening of its entire endocardium. This was especially intense beneath the aortic valve (Fig. 1). The auricles were not abnormal. The foramen ovale and ductus arteriosus were closed. The ascending aorta measured 25 mm. in circumference and showed dilatation of the ostia of all vessels arising in its arch. At the distal portion of the arch, a ridge of thickening abruptly narrowed the lumen to 5 mm., adjacent to the ostium of the obliterated ductus. Beyond this, the aorta widened to 20 mm. (Fig. 2).

Microscopically, the heart showed hypertrophy of its fibers. There was marked fibroelastic thickening of the endocardium of the left ventricle and a slight amount of subendocardial scarring (Fig. 3). The lungs showed extreme chronic passive congestion and a few

small foci of fresh lobular pneumonia with chronic bronchitis. The liver also showed chronic passive congestion.

*Anatomical Diagnosis:* Coarctation of the aorta. Dilatation of vessels arising from aortic arch. Extreme hypertrophy and dilatation of the left ventricle with fibroelastic endocardial thickening. Severe chronic passive congestion, lungs. Chronic passive congestion, liver. Chronic bronchitis; lobular pneumonia.

*Case 2:* N. B.—A80934 was admitted to Harriet Lane Home 10–4–50 at 10 months of age with the complaint of respiratory distress since 4 weeks of age. Two to three weeks prior to admission, became listless and anorexic. As x-rays revealed a large heart, the infant was admitted for observation. Examination showed an enlarged heart; the heart sounds were soft, with a soft systolic murmur heard all over the chest. Breath sounds were harsh and there were many rales over the left side of the chest, and at the right base. The liver was palpable at the level of the umbilicus. Fluoroscopy showed the heart to be enlarged, especially the right ventricle. The right auricle also seemed large. The lung fields were clear. EKG revealed right axis deviation and extreme right ventricular hypertrophy.

The child was placed in continuous oxygen and digitalized with some general improvement in her status. With the clinical impression that this was a case of pure pulmonic stenosis, the child was taken to the operating room on the morning of the 14th hospital day for the purpose of performing a pulmonary valvulotomy. The child did not tolerate the anesthesia; however, the chest was opened, cardiac massage was performed with restoration of the heart beat, and a valvulotomy was done. However, the child had expired and could not be revived.

Autopsy #22674 was performed 10–17–50 by Dr. Paul Griffith 2 hours after death. The body was well developed and well nourished, weighing 7.5 kg., and measuring 72 cm. in length. The heart was greatly enlarged, weighing 140 grams (normal weight at 10 months is 40 grams). The right auricle was not enlarged. The foramen ovale was closed functionally as it was covered by a valve, but a 5 mm. patency behind the valve flap admitted a probe. The right ventricle seemed relatively very small and its chamber was greatly compressed by a convex bulging interventricular septum. The right endocardium was delicate. The left auricle was normal. The left ventricle was greatly dilated as well as hypertrophied. Its septal wall was concave. Its endocardium showed diffuse white opacity and 1 to 2 mm. thickening (Fig. 4). This was most marked in the septal aspect and outflow region. There were subepicardial hemorrhages from the prolonged cardiac massage. The ductus arteriosus showed a slight patency of 2 mm. in diameter. There was marked narrowing of the lumen of the aorta just proximal to the remains of the ostium of the ductus arteriosus. At this point the aorta measured 11 mm. in circumference, the ascending aorta measured 21 mm. and the descending aorta was 16 mm. in circumference. Microscopically, there was diffuse thickening of the endocardium of the left ventricle, composed of fibrous and elastic tissue, similar to the "fibroelastosis" illustrated in the previous case. There was no myocardial scarring, but the subendocardial fibers were large and vacuolated. No fat or glycogen could be stained. Small myocardial veins were prominently dilated.

*Anatomical Diagnosis:* Coarctation of aorta. Left ventricular hypertrophy and dilatation, severe, with compression of the right ventricle. Thickened endocardium, left ventricle. Swelling and vacuolization of subendocardial muscle fibers; dilatation of myocardial veins. Hepatosplenomegaly. Patent ductus arteriosus, slight. History of fibrillation during anesthesia. Left thoracotomy. Right endocardotomy. History of prolonged cardiac massage. Diffuse subepicardial and myocardial hemorrhage. Pulmonary atelectasis.

*Case 3:* P. G.—A77603. First admission to Harriet Lane Home was 4–23–50 at the age of 16 months because of frequent bouts of dyspnea. At 13 months of age, developed spells

of dyspnea. These increased in frequency, and because a heart murmur was heard the child was brought to this hospital. She was seen as an emergency in the cardiac clinic, acutely and seriously ill, in marked heart failure with respiratory difficulty. Blood pressure was 130/100 in the arms and could not be obtained in the legs. Pulse was 164, brachial and radial pulsations were bounding, but the pulsations in the femoral arteries were very weak. The heart was enlarged, sounds of good quality. A loud systolic murmur was heard over the entire precordium. The liver edge was felt 3 fingerbreadths below the costal margin. The splenic tip was also felt. Fluoroscopy showed the heart to be markedly enlarged and the lung fields congested. A barium swallow showed an over-all enlargement of the heart, with marked enlargement of the left auricle. The venous pressure was 290 mm. saline. Because of the serious condition of the child, she was admitted to the ward without further studies, to be digitalized. However, shortly after admission, she became very dyspneic, cyanotic, showed rapid deterioration and expired shortly thereafter. The clinical impression was heart failure due to congenital heart disease; cyanotic tardive; coarctation of the aorta; ? patent ductus; ? septal defect.

Autopsy #22373 was performed 4–24–50 by Dr. Wolfson, 8 hours after death. The body weighed 10 kg., and measured 79.5 cm. in length. Excess fluid was present in both pleural cavities and in the pericardial sac. The heart was enlarged, but not weighed as it was not dissected from the lungs. There was hypertrophy and dilatation of the right auricle and ventricle; and the wall of the pulmonary artery was thicker than the wall of the aorta. The left auricle was dilated and hypertrophied. Its endocardium was thick and opaque. The foramen was closed. The mitral valve was abnormal, with fused cusps and chordae tendineae, and resulting mitral stenosis. There was also hypertrophy of the left ventricle and thickening of its endocardium. Distal to the left subclavian artery the aorta showed a coarctation with its circumference narrowed to 2 to 3 mm. This barely admitted a probe. The ductus was closed, but enlargement of the upper intercostals, bronchial and internal mammary arteries showed the presence of a prominent collateral circulation. Microscopic sections of the heart showed hypertrophied fibers but no scarring suggestive of preceding inflammation. The endocardium of the mitral valve was thickened and its leaflet contained mucoid infiltration. All sections of the left auricle and ventricle showed marked endocardial thickening which in elastic stains was seen to be due to fibrous and elastic tissue proliferation (Fig. 5). The pulmonary artery showed a thickened media containing basophilic mucoid material. Chronic passive congestion was present in the lungs, liver, and spleen.

*Anatomical Diagnosis:* Coarctation of the aorta; enlargement of internal mammary, bronchial and intercostal arteries. Congenital malformation, mitral valve with stenosis. Hypertrophy of both ventricles, dilatation of both atria and right ventricle. Fibroelastic endocardial thickening, left auricle and left ventricle. Chronic passive congestion lungs, liver and spleen. Hydrothorax and hydropericardium.

*Case 4:* Z. D.—A47364. Admitted to the Harriet Lane Home 4–12–27 at 16 months of age, moribund. The baby had been seen with obstruction to breathing at 4 months, thought due to adenoids, and had then been well until 6 days before admission. At that time, developed cough, anorexia and sore tongue. On the morning of admission became much worse and was brought to the dispensary. Was moribund and immediately admitted to the wards with a diagnosis of acute primary pneumonia. Pulse was not obtainable; respiration 66, gasping. All kinds of rales were heard over both lungs. The chest was too noisy to hear the heart sounds, and the pulse was too rapid to count. The edge of the liver was 3 fingerbreadths below the costal margin, and the spleen was felt at the same level. Although nasal oxygen was started at once, the respirations became weaker and irregular, and the patient died about 15 minutes after admission.

Autopsy #9804 was performed 4–13–27 by Dr. McCordock, about 24 hours after death.

The body was well nourished and developed, weighing 10 kg., and measuring 77 cm. in length. The heart was enlarged, weighing 110 grams. (The normal weight for this age is 48 grams). The foramen ovale was widely open. No valvular or myocardial lesion was noted, but the left ventricle was distinctly dilated. The ascending aorta measured 3 cm. in circumference; the ductus was closed; and at its closed ostium the aorta suddenly narrowed to 1.3 cm. in circumference. In the descending portion, the aorta widened to 2.7 cm. The lungs showed widespread consolidation in the left upper and right middle and lower lobes. Microscopically the lungs showed fresh confluent lobular pneumonia. The endocardium of the heart was delicate in all sections (Fig. 6). There were, however, a few small inconspicuous foci of lymphocytes in the epicardium and myocardium.

*Anatomical Diagnosis:* Coarctation of the aorta. Cardiac hypertrophy. Patent foramen ovale. Confluent lobular pneumonia. Slight focal myocarditis. Acute splenic tumor.

*Case 5:* F. J.—A36243. Was admitted to the Harriet Lane Home 6–24–44 at the age of 1 year, 11 months with a right hemiplegia. Polydactilia had been noted at birth. She had been completely well until 5 days before admission, when there was fever, crying spells and inability to stand on the right leg. Examination showed an anemic little colored girl. Respirations 37; pulse 104. Blood pressure was 100/60 in both arms. The heart was enlarged to percussion and the liver edge was palpable. There was no facial paralysis, but there was incomplete hemiplegia of the right arm and leg. During the hospital stay, the blood pressure rose to 130/90. EKG showed normal sinus mechanism. X-rays showed cardiac enlargement; lungs clear. All other tests were negative. The patient was put on digitalis and the hemiplegia improved, although its cause was not discovered. She was discharged after 2 months, to be followed in the cardiac clinic. She soon developed "falling spells", 4 to 5 daily associated with jerking and loss of sphincter control. This was thought to be epilepsy, secondary to the lesion producing the hemiplegia. She was replaced on digitalis as the liver again became enlarged and respirations rapid. Three months after discharge from the hospital, the child seemed feverish and not so well. After breakfast the next day (12–8–44) she vomited 3 times and fell over dead. Her age was 2 years and 4 months.

Autopsy #19238 was performed 12–9–44 by Dr. Harrison Latta 26 hours after death. The child was well developed and well nourished. The heart weighed 155 grams (normal at 28 months is 57 grams). All chambers of the heart were dilated and hypertrophied to a marked degree, and there was marked endocardial thickening throughout. The thickened endocardium appeared white and opaque. The foramen ovale and ductus arteriosus were closed. The left coronary ostium was abnormally large, measuring 5 mm. in diameter and was located high above the sinus of Valsalva. The right coronary ostium was normal. The ascending aorta measured 4 cm. in circumference, and at the level of the closed ductus, the aortic circumference was 2½ cm. The left side of the brain was smaller than the right. There was an extensive old infarct involving the left parietal lobe, leaving a series of cystic cavities in the white matter, and a shallow rim of yellow cortex. The lumen of the left middle cerebral artery was occluded by translucent white material. Microscopically, the heart showed a moderately thick layer of fibroelastic endocardial thickening (Fig. 7). There were no mural thrombi to explain either this thickening or the thrombus found in the middle cerebral artery. This thrombus was now completely organized and recanalized and extended into the small cerebral branches. Microscopically the infarct was also old. There was associated demyelinization of the cortico-spinal tracts. In the lungs, there was extensive confluent pneumonia.

*Anatomical Diagnosis:* Coarctation of the aorta. Cardiac hypertrophy and dilatation. Fibroelastic endocardial thickening. Recanalized thrombus, left middle cerebral artery, with massive old infarct, left parietal region. Demyelinization, cortico-spinal tracts. History

of hemiplegia, followed by partial recovery and convulsions. Confluent lobular pneumonia. Atrophy of central liver cells.

## DISCUSSION

Adult-type coarctation of the aorta is rarely found as the cause of death in infancy. When present in this age period, this lesion usually occurs as an incidental finding, as in Autopsy #9804, and several cases reported in the literature (3–12–14, etc.). In Autopsy #9804, the infant died of an overwhelming pneumonia without previous signs or symptoms referable to coarctation. Similarly in the cases of Calodney and Carson (3), Sala and Nachamie (12) as well as in Wadstein's case (14), the coarctation was not related to death.

There is, however, a group of infants dying in heart failure, or with a previous history of heart failure, showing adult-type coarctation at autopsy. In 3 of the infants previously reported in the literature (4, 8, 15), as well as 4 of the cases herein reported, severe endocardial fibroelastosis was also found in association with the coarctation. A similar situation was seen in the 3 cases of Bahn *et al.* (2).

In view of the occurrence of endocardial fibroelastosis in association with coarctation in these 10 cases, it is interesting to speculate on the pathogenesis of the fibroelastosis, its relation to the coarctation and the cause of heart failure.

The pathogenesis of endocardial fibroelastosis is not clear. Bahn and his associates (2) considered it to be of "secondary nature and a consequence of left ventricular dilatation incident to failure." Gowing (6) has reviewed 76 cases of fibroelastosis reported in the literature and found that less than 10% of these cases occurred in association with other congenital lesions. However, the majority of observers consider fibroelastosis to represent a congenital defect. Its association with coarctation in 4 of the 5 cases herein presented and in 6 of the 14 cases of coarctation in patients under 2 years of age previously reported in the literature suggests that fibroelastosis, too, is an anomaly of development.

There is little basis for considering the fibroelastosis in the 10 cases under discussion as the result of the coarctation. As a control series, 11 cases of coarctation in older children and adults ranging in age from 7 to 58 years were studied. In all of these cases, symptoms of coarctation with hypertension were present prior to death. Seven deaths resulted from post-operative complications following resection of the coarctation; the 4 other cases died as a result of rupture of a congenital cerebral aneurysm. In none of these cases did the heart show fibroelastosis. At most, slight focal endocardial thickening was seen in three cases in association with coronary sclerosis and myocardial scarring. It seems, then, from this series, that even protracted hypertension resulting from coarctation fails to produce endocardial fibroelastosis. In our 3 infants in whom hypertension had been noted during life (Cases 1, 3, and 5), the longest survival following this observation was only 6 months.

In reviewing the literature on adult-type coarctation of the aorta, it is seen that although this condition is frequently recognized clinically at an early age, death due to heart failure is unusual in this age period. In Table I it appears as the stated cause of death in 4 cases; once in association with congenital mitral stenosis and in the 3 cases of Bahn *et al.* These investigators regarded the heart failure as having been caused by "obstructive hypertension". In their 3 cases of coarctation, endocardial thickening was present and as stated above, considered of secondary importance. In each case, the ductus was closed or closing and "there seemed to be inadequate collaterals to by-pass the coarctation" thereby causing "left ventricular strain and hypertrophy and ultimately left ventricular failure".

However, it is well recognized that hypertension and resulting cardiac hypertrophy may be present for many years in cases of coarctation without the development of heart failure. The "adequacy" of the collateral circulation is impossible to demonstrate, and heart failure in cases of coarctation as well as in cases of essential hypertension is due to intrinsic differences in the functional capacity of the cardiac muscle and, of course, to any additional strains imposed upon it (e.g., coronary sclerosis, myocarditis, valvular disease, etc.).

In infancy, endocardial fibroelastosis without other lesions has been shown to be sufficient to produce death from heart failure (Weinberg and Himmelfarb (15), Prior and Wyatt (10), etc.). The mechanism of the production of failure has been discussed in detail by these authors. The latter investigators think that the endocardial abnormality tends to limit diastolic filling and systolic expulsion in a fashion analogous to constrictive pericarditis. In addition, Weinburg and Himmelfarb point out that the thickened endocardium interferes with the emptying of the Thebesian veins into the ventricular cavity, and suggest that the resulting stasis may cause myocardial anoxia and finally heart failure.

In contrast to the situation in endocardial fibroelastosis, cardiac compensation is ordinarily good in infants with an adult-type coarctation; and the complications due to hypertension occur at a much later age period. However, if the added embarrassment of fibroelastosis exists, coarctation assumes a greater importance at an earlier age, and early circulatory failure occurs as a result of this double strain. This is shown in Autopsies 19238, 22674, and 24044. In Autopsy 22373, congenital mitral stenosis also participated in the production of failure.

## SUMMARY

1. Five cases of adult-type coarctation occurring in infancy are reported, with associated endocardial fibroelastosis occurring in 4 of the cases.

2. The association of endocardial fibroelastosis with coarctation and other malformations, as reported here and in the literature, lends weight to the view that it, also, is due to a developmental defect.

3. The rarity of coarctation, alone, as cause of heart failure in infancy, suggests that in the present cases, failure was due to the double strain of the endocardial fibroelastosis and coarctation. In one case, congenital mitral stenosis was also a precipitating factor in the final heart failure.

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## EXPLANATION OF PLATES

(Photographs by Mrs. Joan Bailey)

All sections were stained by the Verhoeff Van Giesen method. All microphotographs are low power and taken at the same magnification

### PLATE I

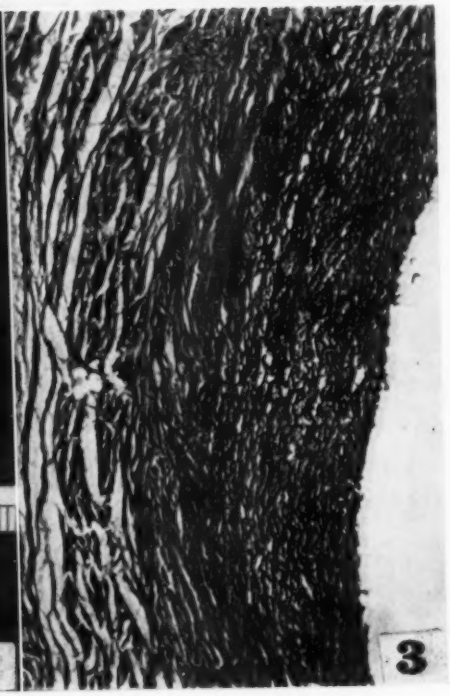
Fig. 1. Case 1: Autopsy 24044: Hypertrophy of left ventricle with thickening and opacity of endocardium.

Fig. 2. Adult-type coarctation; Case 1: Autopsy 24044. Note dilated ostia in arch and descending aorta.

Fig. 3. Microscopic appearance of thickened left ventricular endocardium in Fig. 1. There is proliferation of elastic fibers as well as connective tissue. There is also some subendocardial scarring. Dilated Thebesian veins are seen in the myocardium. Compare with Fig. 6.

24044
1

24044
METRIC
2


3

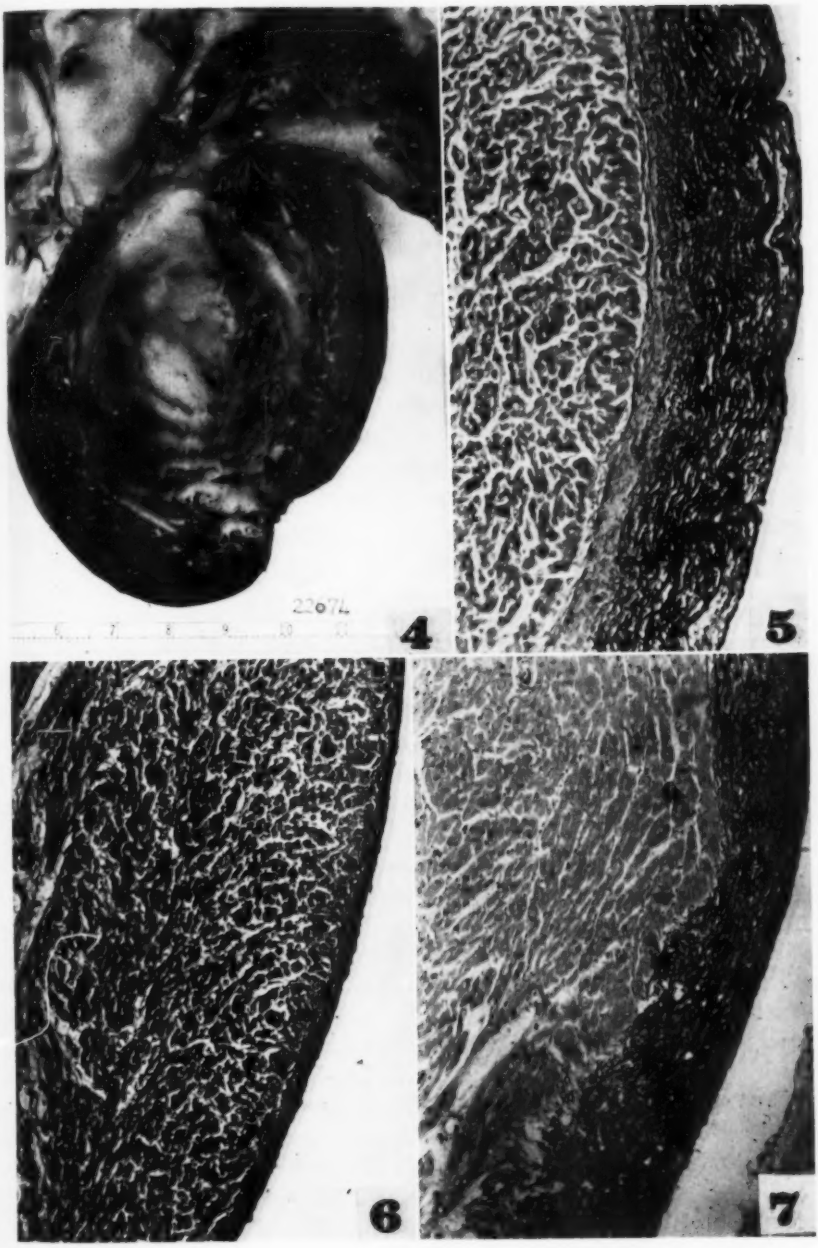
## PLATE II

FIG. 4. Case 2: Autopsy 22674: Hypertrophy of left ventricle with opaque thickening of its endocardium.

FIG. 5. Case 3: Autopsy 22373: Microscopic appearance of endocardium of left ventricle, showing fibroelastic thickening.

FIG. 6. Case 4: Autopsy 9804: A 16 months infant with adult-type coarctation, dying of acute pneumonia. This infant never showed any signs of heart failure. Note thickness of normal endocardium lining left ventricle.

FIG. 7. Case 5: Autopsy 19238: Endocardium of left ventricle, showing fibroelastic thickening.


22674
4
5
6
7

# A STUDY OF THE RÔLE OF ADRENOCORTICOTROPIC HORMONE (ACTH) IN THE PATHOGENESIS OF TUBULAR DEGENERATION OF THE ADRENALS

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Several years ago, one of us (1) directed attention to a peculiar type of adrenal cortical damage that occurs in severe acute infections, and pointed out that when the lesion is extensive it is commonly accompanied by peripheral circulatory collapse. It was also pointed out that the typical Waterhouse-Friedrichsen clinical syndrome, particularly when occurring in adults, is often associated with this adrenal lesion in the absence of the extensive adrenal hemorrhage to which the circulatory collapse of that syndrome is ordinarily attributed.

The lesion, which was termed "tubular degeneration" of the adrenal cortex and was amply described and illustrated in the paper referred to (1), consists essentially in scattered necroses of single or several cortical cells, shedding of the vacuolated cytoplasm of others, and exudation of fluid from adjacent capillaries into the cortical cell cords, with the resulting conversion of the normally solid cords of cortical cells into tubular structures lined by flattened cells which have lost much of their cytoplasm. The lumina of the "tubules" may appear empty or may contain protein, fibrin, a few polymorphonuclear leucocytes and occasional necrotic cortical cells. A search of the literature showed that this lesion had been noted by several observers earlier in the century (literature in ref. 1), but their mention of it attracted scant attention then or subsequently, and too little was known about the functions of the adrenal cortex at that time to permit any suggestion of the possible relation of the lesion to circulatory collapse. When this lesion is well developed and extensive, the damage to the cortical cells is such that there can be little doubt that the function of the cortex must be greatly impaired; and in the light of present knowledge relating to the rôle of the adrenal cortex in the maintenance of the blood pressure, it is reasonable to believe that the peripheral circulatory collapse that is commonly associated with extensive tubular degeneration may be due in part, if not in some cases entirely, to the depression of adrenal cortical function produced by this grossly damaging lesion. This is particularly probable since it has been shown by Thorn (2) and others that during acute infections the amount of cortical hormone required to prevent circulatory collapse is greatly increased. If tubular degeneration is present, the severely damaged adrenal cortex may be unable to respond adequately to this greatly increased demand for cortical hormone.

What is the pathogenesis of this adrenal lesion? Since the prime condition under which it occurs is severe acute infection, one possibility is that the damage to the cortical cells is a direct effect of noxious bacterial products. This is the explanation ordinarily invoked to account for the focal injury and necrosis of liver cells that occurs during a wide variety of severe acute infections, though in the case of the liver, as well as the adrenal, it is not clear why the damage is focal or, indeed, just what the noxious bacterial products are which produce the damage in most of the infections in which it occurs.

Since the adrenal lesion under discussion occurs in a wide variety of infections, a second possibility is that it is a result not of a direct toxic action of bacterial products, but of some bodily factor that is brought into play by the state of severe acute infection. One such factor is the above-mentioned demand for increased functional activity that is placed upon the adrenals during the stress of severe infection. Can the adrenal be goaded by the pituitary adrenocorticotropic hormone to such an intense degree of activity that its cells become damaged and even necrotic, and if so would such overstimulation result in the lesion of tubular degeneration?

In their monograph on the experimental morphology of the adrenal cortex, Selye and Stone (3) pictured a condition somewhat similar to tubular degeneration, produced in rats "chronically treated with crude anterior-pituitary extracts". They regarded the lesion as being a result of exhaustive stimulation. According to Sayers (9), "the crude extracts (of the pituitary) prepared by Dr. Selye contain little or no ACTH activity". Ingle (4), furthermore, has pointed out that pituitary glands obtained from the salughter house are heavily laden with bacteria, and that in his and in Selye's experiments the injection of the suspensions produced abscesses in the rats. No details of the experiments of Selye and Stone were published, but Dr. Selye (5) has kindly replied to our inquiry with the information that the most consistently positive results were obtained by treating rats with daily injections of lyophilized anterior pituitary material for three weeks, after which they were exposed to a sudden stress (cold, several subcutaneous injections of formalin) which was sufficiently severe to kill some of the animals. The anterior pituitary material was contaminated with bacteria, but infection was believed not to have been responsible for the adrenal lesion, for injections of lyophilized liver or kidney did not produce the lesion. It is stated in the monograph of Selye and Stone (3), however, that they were able to produce the lesion by infection.

Since severe acute infection is the commonest cause of tubular degeneration of the adrenals in the human being, and since the material which produced a similar lesion in the adrenals illustrated by Selye and Stone was heavily contaminated with bacteria and, according to Selye (8), produces abscesses in addition to containing much toxic protein material as well as all of the other pituitary hormones, it was desirable to determine whether excessive stimu-

lation of the adrenal cortex by sterile, more purified adrenocorticotropic hormone could produce the lesion and, if so, what amount of the hormone would be required and how rapidly the lesion could be induced to develop; for in the human being no long-period preparation of the adrenal is necessary for the development of tubular degeneration. The lesion can occur rapidly in the face of infection. It may, for example, be found at autopsy in patients who have died within 48 hours after the onset of symptoms of fulminant meningococcal infection. It was desirable, therefore, to learn whether intense stimulation of the adrenal cortex by adrenocorticotropic hormone in the absence of infection could produce the lesion in a comparable time. In their monograph, Selye and Stone (3) mention, with no details, that they produced a similar lesion in rats with estrone, estradiol, stilbestrol and corticotrophin. Bergner and Deane (6), however, found no such lesion in rats treated with 12 mgm. of ACTH per day for 12 days. Shaberg (7) described small focal hemorrhages associated with necrotic cells in the adrenal cortex of guinea pigs treated with 30 mgm. of ACTH during 24 hours. His illustrations show no tubular degeneration.

## EXPERIMENTS

Adult male Wistar albino rats, obtained from the Research Supply Company, Philadelphia, were the experimental animals. They were received in shipments as needed, and were kept in separate cages in the same room for at least several days before being used. Ralston's Purina Laboratory Chow and water was supplied *ad libitum* before and during the experiments. The body weights at the beginning of the experiments are listed in Table I. Armour's beef ACTH, a lyophilized sterile powder in individual vials, each containing an amount of ACTH standardized in equivalents of the Armour LA-1-A standard, was used throughout. This ACTH, according to the Armour Laboratories, was free from contamination with thyrotropic, somatotrophic and gonadotropic hormones. Six different lots were used in the experiments, which may account in part for the occasional irregularities in Table I. The daily amount of ACTH listed in Table I was given in four divided doses, the injections being made subcutaneously every six hours around the clock, using a sterile tuberculin syringe and 26 gauge needles. The amount of ACTH required at each injection time was freshly dissolved in sterile saline that was introduced into the vials in appropriate amount. When all of a prepared solution was not used at a given injection time, the excess was kept in the ice box for the next injection. No solution was kept longer than six hours before being used.

In the first two experiments the total amount of fluid to be injected at each time period was deposited at one site, though a different site was used for each injection. In subsequent experiments the fluid given at each period was injected at two to four separate sites to facilitate absorption. The amount of fluid deposited at each site was 0.25 to 0.5 cc., usually the former. Preliminary to the injections the hair was plucked or shaved, and the injection sites were swabbed with 70% alcohol.

Table I is a composite of twelve separate experiments, in each of which two to nine animals received ACTH. In order to have a check on the effect of the handling of the animals and the trauma incident to the repeated injections, in all but two of the experiments controls were injected with sterile saline in the same volume and at the same times as the ACTH solution administered to the test animals, and they were killed together with their

respective test mates. In some of the experiments there was a saline-injected control for each animal that received ACTH. In other experiments a single control was used for each

TABLE I

*Effect of ACTH upon the Adrenal Cortex of the Rat*

| RAT NO.[1] | BODY WT. GMS. | DAILY MGM. ACTH | DAILY MGM. ACTH PER 100 GMS. BODY WT. | NO. OF DAYS ACTH | DECREASE IN FINE LIPID DROPLETS | COLLOID GLOBULES | LARGE CYTOPLASMIC VACUOLES | NECROSIS OF INDIVIDUAL CELLS | TUBULAR DEGENERATION | FOCAL HEMORRHAGE |
|---|---|---|---|---|---|---|---|---|---|---|
| 61R | 200 | 12.5 | 6.2 | 1 | + | 0 | 0 | 0 | 0 | 0 |
| 62R | 230 | 12.5 | 5.4 | 1 | ++ | 0 | 0 | 0 | 0 | 0 |
| 108U | 178 | 12.5 | 7.0 | 1 | ++ | 0 | 0 | 0 | 0 | 0 |
| 67R | 234 | 12.5 | 5.3 | 2 | +++ | 0 | 0 | 0 | 0 | 0 |
| 68R | 224 | 12.5 | 5.5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| 111U | 180 | 12.5 | 6.9 | 2 | +++ | 0 | 0 | 0 | 0 | 0 |
| 69R | 236 | 12.5 | 5.3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 70R | 230 | 12.5 | 5.4 | 3 | + | 0 | 0 | 0 | 0 | 0 |
| 116U | 184 | 12.5 | 6.8 | 3 | ++++ | 0 | 0 | 0 | 0 | 0 |
| 73R | 256 | 12.5 | 4.9 | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| 74R | 256 | 12.5 | 4.9 | 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| 117U | 179 | 12.5 | 7.0 | 4 | ++ | 0 | 0 | 0 | 0 | 0 |
| 57R | 198 | 25.0 | 12.6 | 1 | ++ | 0 | 0 | 0 | 0 | 0 |
| 58R | 210 | 25.0 | 11.9 | 1 | ++ | 0 | 0 | 0 | 0 | 0 |
| 105U | 178 | 25.0 | 14.0 | 2 | ++++ | 0 | 0 | 0 | 0 | 0 |
| 106U | 176 | 25.0 | 14.2 | 3 | ++++ | + | + | 0 | 0 | 0 |
| 107U | 174 | 25.0 | 14.3 | 4 | +++ | + | + | 0 | 0 | 0 |
| 44R | 180 | 50.0 | 27.7 | 1 | +++ | +++ | +++ | + | + | 0 |
| 53R | 216 | 50.0 | 23.1 | 1 | ++ | + | + | + | + | 0 |
| 54R | 210 | 50.0 | 23.8 | 1 | +++ | ++ | ++ | + | + | 0 |
| 168T | 178 | 50.0 | 28.0 | 1 | + | ++ | 0 | 0 | 0 | 0 |
| 1P | 290 | 50.0 | 17.2[2] | 2 | + | ++++ | 0[2] | 0 | 0[2] | 0 |
| 2P | 300 | 50.0 | 16.6[2] | 2 | ++++ | ++++ | 0[2] | 0 | 0[2] | 0 |
| 45R | 172 | 50.0 | 29.0 | 2 | ++++ | + | ++ | + | +++ | 0 |
| 162T | 166 | 50.0 | 30.1 | 2 | +++ | +++ | ++ | + | + | 0 |
| 48R | 178 | 50.0 | 28.0 | 3 | ++ | ++ | ++++ | + | ++++ | 0 |
| 49R | 178 | 50.0 | 28.0 | 3 | ++ | ++++ | ++++ | + | ++++ | + |
| 20Q | 186 | 50.0 | 26.9 | 4 | + | ++++ | +++ | + | +++ | 0 |
| 21Q | 180 | 50.0 | 27.7 | 4 | +++ | + | ++++ | + | ++++ | + |
| 46R | 182 | 50.0 | 27.4 | 4 | + | ++ | ++++ | + | ++++ | + |
| 47R | 160 | 50.0 | 31.2 | 4 | ++ | +++ | ++++ | + | ++++ | + |
| 77S | 210 | 50.0 | 23.8 | 4 | + | +++ | +++ | + | +++ | + |
| 163T | 178 | 50.0 | 28.0 | 4 | 0 | ++ | +++ | + | +++ | + |
| 165T | 180 | 50.0 | 27.8 | 4 | 0 | ++ | +++ | + | +++ | + |

[1] The animals with the same letter after their number received ACTH from the same lot.

[2] This animal, because of its greater weight, received decidedly less ACTH per 100 gms. of body weight than did the others that received the same total dosage. Furthermore, being one of the first used, each injection dose was deposited at one site instead of distributed at several sites as was subsequently done to promote absorption.

two test animals. In addition to the dosages of ACTH shown in Table I, daily doses of 100 mgm. were given to two rats for one day, to one rat for two days, and to two rats for four days. There was no significant macroscopic or microscopic difference between the

adrenals of these animals and of those that received the 50 mgm. daily dose. There were, in all, 39 ACTH-injected test animals and 25 saline-injected controls.

The animals were routinely killed by etherization in a glass jar, except in the case of several which were killed by drowning. All test animals and controls were killed six hours after the last injection and were immediately autopsied. The tissues for routine sections were ordinarily fixed for 4 hours in Zenker-formol, followed by 6 hours fixation in 10% formalin, after which they were washed in running water for 6 hours before being placed in 80% alcohol to begin dehydration for paraffin embedding. Glands preserved for fat stains (Sudan IV) were fixed in 10% formalin. Routine sections were made from the adrenals and from thin slices of the liver, spleen, pancreas and kidneys. Numerous subcutaneous sites where the ACTH was injected were studied microscopically (hematoxylin-eosin and bacterial stains), and the lungs and hearts of some of the animals were also sectioned and studied. The other tissues were preserved in 10% formalin. The adrenals were removed with great care to avoid any mechanical injury, and were fixed entire. It was soon found that the escape of blood from the severed adrenal vessels prevented a proper microscopic evaluation of the degree of hyperemia produced by the ACTH stimulation. Thereafter, the adrenal vessels were carefully ligated, and the glands were removed and fixed with the attached ligated vessels. This gave a far better histological picture of the relation of the parenchyma to the vascular supply. Since our chief interest lay in the histological alterations in the adrenals, the glands in most instances were not weighed at autopsy, for it was desired to subject them to as little manipulation as possible and to fix them as promptly as possible. The skin of each animal was reflected at autopsy to permit examination of the subcutaneous injection sites. The absorption at each site was almost always excellent. Often there was no macroscopic evidence of the injected solution, and at the most there was only a slight, pale yellowish discoloration which sections showed to represent unabsorbed remains of the injected material and a slight to moderate inflammatory exudation. There was virtually no reparative process at the sites of injection in the animals receiving 50 mgm. per day, and only a slight one in those that received 12.5 mgm. or 25 mgm. per day.

In none of the experiments did the injections of ACTH produce any recognizable alterations in the cells of the adrenal medulla, the liver, pancreas, kidneys or the blood vessels in the sections studied. Loss of lymphoid cells was evident in the spleens of the more intensively treated animals.

*12.5 mgm. ACTH daily.* The adrenals of three of the six animals treated with this dosage for one and two days appeared slightly larger on gross inspection than those of the saline-injected controls. The adrenals of two of the animals treated for three days appeared essentially normal; those of the third animal appeared slightly larger than normal. The adrenals of two of the animals treated for four days with this dosage appeared larger and more hyperemic than those of the controls; those of the third animal did not differ appreciably from the controls.

Microscopically there were no cellular abnormalities in the adrenals of any of these animals, other than a decrease in the number of the small cytoplasmic lipid droplets that are normally present in the cortical cells. Since the "stress" of handling and trauma, incident to the repeated injections of ACTH, might cause some degree of discharge of lipid from the cortical cells, the content of

lipid droplets in the cells of the test animals was always compared with that in controls, which were subjected to injections of the same volume of sterile normal saline at the same periods and for the same number of days. The degree of decrease in lipid droplets listed throughout Table I represents an estimate of the degree of difference between the test animals and the respective controls. The decrease varied from a moderate difference (+ in Table I) to a virtually complete disappearance of the droplets (++++ in Table I). Eight of the twelve test animals that received 12.5 mgm. of ACTH daily showed varying degrees of loss of lipid droplets, as compared with the controls, but there was no consistent correlation between the degree of loss of lipid and the amount or duration of ACTH treatment.

*25 mgm. ACTH daily.* The adrenals of the animals treated with this dosage for one day were not appreciably different macroscopically from their controls. Those of the animals treated for two, three and four days were hyperemic and definitely larger than their controls.

Microscopically, the cortical cells of all of the ACTH treated animals of this group showed a decrease in lipid droplets, which reached a virtual absence in two of the animals (Nos. 105 and 106). There were no other cellular abnormalities in the cortices of the animals treated for one and two days, but in the animals treated for three and four days there were eosinophilic colloid globules in occasional cells of the fasciculate zone, and the cytoplasm of a few fasciculate zone cells was largely replaced by a single vacuole of the type described below.

*50 mgm. ACTH daily.* The adrenals of all animals treated with this dosage were hyperemic and decidedly larger than their controls, the glands of animals treated for 4 days being several times the normal size. The adrenal veins were correspondingly engorged.

Microscopically, the cortical cells of all animals showed a decrease in lipid droplets as compared with their controls. They were virtually absent in two of the animals (Nos. 2 and 45). Colloid globules (Figs. 10, 11, 12) were present in varying degree in the cortical cells of all of the test animals, and in some of the animals there were, in the zona fasciculata, cells with non-vacuolated but coarsely spongy cytoplasm, and others with a reticulated cytoplasm, the reticular threads simulating fibrin.

The most striking alterations in this group were the occurrence of single, very large vacuoles in the cortical cells, and the results of the rupture and confluence of the vacuoles of adjacent cells. Often there remained only a thin layer of cytoplasm about the vacuole. The fluid in the vacuoles was not sudanophilic. When the confluence of vacuoles involved only a limited number of cells in a given area it resulted in the formulation of circumscribed cavities or tubules, which were often lined by cells that had lost much of their cytoplasm in the process. Single dead cells were also found here and there at the margins of the

cavities or shed into the lumina (Fig. 4). When marginal cells were lost in this manner, fluid and occasional leucocytes often escaped into the cavities from the adjacent capillaries and threads of fibrin were present in some of them. When this cavitation was extreme, the cortex in the affected region was transformed into irregularly anastomosing strands of capillaries and cortical cells, many of which had lost much of their cytoplasm (Fig. 8). These distorted strands of cortical cells and capillaries were widely separated by irregular spaces containing either no stainable material or else coagulated protein and occasional leucocytes and dead cortical cells, or even hemorrhage. The large vacuoles, their intercellular confluence, and the formation of tubules and irregularly anastomosing cavities, first made their appearance in the inner portions of the cortex and were always more marked in this region. In the more severely affected adrenals the process extended, in places, throughout the fasiculate zone, and in small, focal areas involved the glomerulosa as well. It may be mentioned that in the human being tubular degeneration ordinarily begins and is most prominent in the outer third of the fasiculate zone.

In most of the more severely affected adrenals there were small, focal hemorrhages in the cortex which, in several instances, were widespread.

## DISCUSSION

These experiments demonstrate that marked overstimulation of the adrenal cortex by the pituitary adrenocorticotropic hormone (ACTH) can produce profound alterations in the cortical cells and in the structure of the cortex, resulting in the formation of lesions which reproduce the essential features of the peculiar "tubular degeneration" of the cortex that commonly occurs during fulminant acute infections in the human being (1). The ACTH used in these experiments was sterile, the injections were made under aseptic precautions, and the injection sites were uninfected. It is therefore clear that neither infection nor toxic bacterial products are necessary for the production of this damaging adrenal cortical lesion, and it becomes probable that the occurrence of tubular degeneration during severe acute infections in man results not from a direct action of toxic bacterial products upon the adrenal cells, but from excessive hormonal stimulation of the cortical cells under the stress and conditions of severe acute infection. The experiments also show that the lesion can develop rapidly under ACTH stimulation. As was mentioned in the introduction of this paper, tubular degeneration may be found at autopsy in cases of fulminant acute infection as early as 48 hours after the onset of symptoms. In this study, in some of the animals the lesion had begun to appear at 24 hours, and was well marked at 48 hours, after beginning the administration of the larger dosages of ACTH.

The amount of ACTH that was required to produce adrenal tubular degeneration in rats under the conditions of these experiments was very large, and if

calculated simply in relation to body weight it is obvious that the human pituitary could not secrete such an amount of the hormone daily. There are, however, important considerations which render inadmissible a conclusion based only upon the relation between body weight and the amount of ACTH used in these experiments.

In the first place, the ACTH used in the present experiments was, of course, not chemically pure, and was therefore far less potent, weight for weight, than the pure, endogenously produced hormone. Indeed, a more highly purified (but still not chemically pure) ACTH that has recently been obtained from the pituitary is, weight for weight, about 150 times more effective therapeutically in the human being than the ACTH used in the present experiments. Amounts of this more purified ACTH as small as 0.19 mg. daily, administered subcutaneously, have produced signs of hyperadrenalism (moon face, hirsutism, marked water retention) (22).

In the second place, it is now well known that a given amount of ACTH exerts a much greater effect when administered by continuous intravenous drip, which roughly simulates the natural process of its secretion into the blood stream, than it does when injected intramuscularly, or subcutaneously as in the present experiments. It is, furthermore, estimated that when the type of ACTH used in these experiments is injected into the tissues, at least 67% of it is inactivated and does not reach the adrenals in active form (24). Gordon and his coworkers (12) have estimated from their studies that the intravenous infusion of ACTH could be as much as 20 times more effective therapeutically than the intramuscular injection of the same dose. This has been confirmed by others (24); and recently Bates (23) found the intravenous route of administration to be 100 to 1,000 times more effective than subcutaneous injection in causing an equivalent ascorbic acid depletion of the adrenal cortex.

In the third place, too little is known about species differences in the responsiveness of the adrenal to ACTH to permit one to calculate the amount that would be required to produce a given effect on the human adrenal simply by multiplying the amount used in the rat by the ratio of the body weight of man to that of the rat. That species differences in the responsiveness of the adrenal cortex to adrenocorticotropic hormone exist is indicated by Blumenthal's (25) observation that the cortex of the rat is less responsive to this hormone than is that of the guinea pig. Furthermore, Kass (20) has reported that mice tolerate, without evidences of toxicity, a daily dosage of ACTH equivalent, on the basis of body weight, to *8 grams* per day for the human adult; and Schoenbach (21) has given to mice much larger daily doses than even that, without observable toxic effects. Indeed, differences in the responsiveness of the adrenal to ACTH occur even within the same species. Woods (13), for example, has found that it requires a much greater amount of

ACTH to produce a given reduction of adrenal ascorbic acid in the wild Norway rat than in the domesticated one.

Finally, and important for the present consideration, Conn (10) has aptly pointed out that conditions of stress (and fulminant febrile infection is a severe stress) may bring about the liberation not only of ACTH, but of other pituitary hormones as well, and the latter may influence the effect of the endogenously produced ACTH,—a modifying influence which the injection of commercial ACTH into a normal animal would not entail. Conn (10) recalls, in this connection, that epinephrine causes the simultaneous discharge of both ACTH and thyroid stimulating hormone from the pituitary. It is well known that epinephrine is liberated under a wide variety of stresses; and Selye (11) has obtained evidence that thyroxin greatly enhances the effect of pituitary extracts upon the adrenal cortex. A given amount of ACTH liberated from the pituitary under the stress of severe infection may, therefore, produce a greater effect upon the adrenal cortex than the same amount injected into the normal body. The ACTH used in the present study was free from contamination with thyrotopic, somatotropic and gonadotropic hormones.

These considerations make it very clear that one cannot estimate the amount of endogenously liberated ACTH that would be required to produce adrenal tubular degeneration in the human being simply by multiplying the body weight of man by the amount of the commercial ACTH injected subcutaneously per gram of rat in the present experiments. But it may be remarked that even on the basis of body weight equivalents calculated in relation to the smallest amount of ACTH that produced the lesion in the present experiments, a correction for the difference (obtained by the ascorbic acid depletion assay) between the potency of the preparation of ACTH used in these experiments and that of the more purified product (22), and for the difference in effectiveness between the intravenous and the subcutaneous routes of injection (23), would give a figure of only 0.17 mg. for the amount of the hormone that would have to be liberated into the blood stream during 24 hours from the pituitary of an adult human being in order to produce the lesion, —and the naturally secreted hormone must be even more potent, weight for weight, than the still impure preparation of ACTH upon which this calculation is based. A calculation of this sort, of course, represents only a very rough and speculative estimate and, besides, is based upon the amount of ACTH required to produce the lesion in the non-infected body of the rat. Since the present experiments demonstrate that infection is not necessary for the production of this peculiar lesion in the rat, and that it can be produced by ACTH, it is reasonable to believe either that during fulminant acute infection the pituitary can produce sufficient ACTH to cause the lesion, or else that severe infection creates additional alterations in the *milieu intérieur* which potentiate the

action of ACTH upon the adrenal cortex and render the amount that the pituitary can produce under stress sufficient to cause the lesion. It will be of interest to learn whether, in the face of a degree of infection insufficient to cause the lesion, and also in noninfected animals under thyroid stimulation, tubular degeneration can be produced by amounts of ACTH smaller than those that were required to produce it in the normal animals used in these experiments.

It is well known that hyperplasia of the adrenal cortex occurs during the reaction to stress and following the injection of corticotropin (14), and it may be mentioned that an increase in *mitosis* in the cells of the fasciculate, and even the glomerular zone was evident in numerous animals that received ACTH in these experiments. This was particularly striking in those that received the larger doses for two or more days. It is reasonable to believe that the stimulus to increased activity provided by the ACTH was primarily responsible for initiating this hyperplasia, for there was no evident correlation between the number of mitoses and the number of necrotic or damaged cortical cells. It should be emphasized, however, that the increase in the size of the adrenals which resulted from the injection of ACTH in the present experiments was not simply the result of an increase in the number of cortical cells. Much of the gross enlargement observed following the larger doses was due to the marked hyperemia, to enlargement of cortical cells resulting from an increase in cytoplasm and from large cytoplasmic vacuoles of fluid and inclusions of colloid, and to the accumulation of fluid in the tubular formations and between the widely separated cell strands in the more severely affected portions of the cortex.

*Colloid globules* of the same appearance as those in the cortical cells of all of the animals that received the larger amounts of ACTH in the present experiments (Table I and Figs. 10, 11, 12), are only occasionally found in the human adrenal cortex (Fig. 9). We have encountered them in such widely different conditions as streptococcal meningitis (Autop. 24,079), chronic renal failure (Autop. Outside W. A.), death in utero from massive subarachnoid hemorrhage during high mid-forceps delivery (Autop. 13,910), diphtheritic tonsilitis and pneumonia (Autop. 15,925), in one (Accession 164,079) of a series of cases of death from exposure to cold studied at the Armed Forces Institute of Pathology through the courtesy of Brigadier General Elbert DeCoursey, and, interestingly, in an adrenal removed surgically from a patient with Cushing's syndrome (S. P. 50-3089-1). Since these experiments show that overstimulation of the cortical cells by the injection of ACTH can cause the appearance of these colloid globules, it would seem reasonable to believe that their occurrence in the human being is indicative of a pituitary overstimulation of the adrenal cortex; but the conditions that determine their occurrence in some cases of overstimulation in disease and not in others remain to be discovered. The precise chemical nature of these colloid globules is not known at present; and the

same may be said of the fluid which fills the large cytoplasmic vacuoles in the adrenals subjected to intense stimulation by ACTH. These are matters requiring further investigation.

During severe acute infections in the human being, *basophilic bodies* commonly appear in the cytoplasm of the hepatic and adrenal cortical cells. Rich and Berthrong (15) have pointed out the occurrence of precisely similar cytoplasmic bodies in the overactive cells of the reticular zone of the adrenal in cases of the adrenogenital syndrome, and have demonstrated the presence of ribonucleic acid in these bodies both in severe infections and in the adrenogenital syndrome. It is of interest that no such bodies made their appearance in any of the cells of the adrenal cortex in present experiments in which the animals were subjected to degrees of adrenal cortical stimulation ranging from mild to very intense. We have carried out no study to determine whether these basophilic bodies appear in the cortical cells of the rat during infection.

The fact that the *zona glomerulosa* remains relatively intact in the hypophysectomized animal, whereas hypophysectomy causes the fasciculata and reticularis to undergo marked atrophy, has led some to believe that the zona glomerulosa functions autonomously, and independently of pituitary corticotropic hormone, and that ACTH acts only on the inner zones of the cortex. Selye and Stone (3) do not share that opinion; and Jones (18) has reported that following hypophysectomy in the mouse, the normally present stainable lipid disappears from the persisting zona glomerulosa, and that it reappears in this zone if the hypophysectomized animal is treated with ACTH, indicating that the zona glomerulosa in that species, responds to stimulation by ACTH. Greep and Deane (19), on the contrary, found no decrease in the lipid of the glomerulosa in the hypophysectomized rat. In acute experiments, Ducommun and Mach (17) noted a decrease in lipid droplets in the zona glomerulosa of normal rats given 2 mgm. of ACTH per 100 gms. of body weight and killed at intervals up to 24 hours after the injection, but they concluded that the decrease was much less pronounced in the glomerulosa than in the other zones of the cortex. Bergner and Deane (6) found no lipid alteration in the zona glomerulosa, and no significant alteration in electrolyte excretion (which is believed by many to be regulated by the secretion of the glomerulosa cells) in normal rats given either 4.5 mgm. of ACTH per 100 gms. of body weight during 24 hours, or about 5.5 mgm. per 100 gms. of body weight daily for 12 days,—doses which did produce a loss of lipid in the zona fasciculata. They concluded that their observations "are compatible with earlier studies which indicated that the glomerulosa is independent of pituitary control in the rat." It is of interest in this connection, therefore, that the administration of larger doses of ACTH in the present experiments has caused a decrease in lipid droplets and the appearance of increased mitoses and colloid globules in the cells of the zona glomerulosa (Figs. 11, 12) as well as in those of the zona fasiculata. Since there is good reason to

believe that the appearance of mitoses and colloid globules in these experiments was the result of a direct action of the ACTH upon the cortical cells, the occurrence of these alterations in the glomerulosa indicates that, in the rat, this zone is not indifferent to the action of ACTH.

Selye (3) lists a variety of well-recognized morphological alterations of the adrenal cortex [atrophy; hyperemia; hypertrophy; hyperplasia; storage or discharge of lipids, cholesterol, colloid, Schiff positive material, and ascorbic acid; reticulation of the cytoplasm; focal necrosis; hemorrhage; and tubular degeneration; (we need not discuss here other listed alterations, such as the occurrence of lymphoid or myeloid foci, for Selye's suggestion that these result from metaplasia of adrenal cortical cells is certainly not established; nor the ill-defined "chromidiosis", which he states may be only a postmortal artefact)], and he concludes that "the very existence of these manifold reaction-forms clearly demonstrates that the structure of the adrenal cortex cannot depend exclusively upon the action of a single corticotrophic hormone", and "is incompatible with the view that all stimuli, which affect the adrenal cortex, act merely by increasing or decreasing the production of a single corticotrophic hormone (ACTH)". This is advanced in support of his concept "which postulates the *existence of several, qualitatively different, corticotrophic agents*" (Selye's italics).

The fact that a variety of cortical morphological alterations occur cannot be accepted as evidence for the existence of a plurality of adrenocorticotropic hormones, for all of these alterations can be produced experimentally by regulating the amount of ACTH to which the adrenal cortex is exposed. Thus, the elimination of ACTH by hypophysectomy produces cortical atrophy, and the cortex can then be restored to normal by the injection of ACTH (16). As for the other cortical alterations, it is known that the amount of cortical ascorbic acid, lipid, cholesterol and Schiff-positive material is readily influenced by ACTH; that the injection of ACTH can produce cortical hyperemia, hypertrophy and hyperplasia; and in the present experiments the injection of ACTH has produced hyperemia, hypertrophy, hyperplasia, alterations in the content of lipid, cytoplasmic reticulation, colloid globules, focal necrosis, hemorrhage, and tubular degeneration. While these observations cannot exclude the possibility that there may be more than one adrenocorticotropic hormone, the fact that the various morphological changes listed by Selye can be produced by the injection of ACTH, at least renders it unnecessary to postulate the existence of several, qualitatively different, corticotropic hormones in order to account for these alterations. Evidence of a different character will be required for proof of the existence of a plurality of adrenocorticotropic hormones. This does not, of course, imply that the action of ACTH upon the adrenal cortex is not influenced, both in character and degree, by other bodily conditions. Quite the contrary, there is reason to believe that it is so influenced, for the action of

other hormones can be influenced by bodily conditions, e.g., by the state of nutrition and the available metabolites, by the activity of other hormones, by the demands of the tissues, etc.

It was pointed out by one of us (1) that the adrenal damage represented by tubular degeneration is particularly common in severe acute infections, and that it may play an important rôle in the pathogenesis of some of the instances of circulatory collapse that occur in fulminant acute infections. When this lesion is extensive it is clear from the marked loss of cytoplasm of many cortical cells, and the necrosis of others, that the functional capacity of the adrenal cortex must be decidedly impaired (fig. 7); and since it has been established that in severe acute infections an increased amount of cortical hormone is required in order to maintain the blood pressure at a normal level (2), a cortex severely damaged in this manner may well be unable to produce the increased secretion essential for maintaining the blood pressure. In such an emergency, the administration of cortical hormone could well be a life saving measure; but since the present experiments show that an excess of ACTH can produce this cortical lesion, the administration of ACTH to a patient with adrenals already damaged in this manner by excessive adrenocorticotropic stimulation arising from the stress of fulminant infection, could serve to increase the damage and to intensify the cortical insufficiency.

The effect of severe tubular degeneration upon the blood pressure in the face of infection, and the effect of tubular degeneration upon the ability to withstand infection and other forms of stress, are important questions that are obviously attackable experimentally by the present method of producing the lesion, and we have begun studies directed toward those ends.

## SUMMARY

Tubular degeneration of the adrenal cortex, which occurs not infrequently in severe acute infections and probably plays an important rôle in the pathogenesis of some of the instances of circulatory collapse that occur in severe infection, can be produced experimentally in the rat by excessive stimulation of the cortex resulting from the administration of large doses of sterile ACTH. The experiments demonstrate that neither the state of infection nor a direct action of bacterial toxic products upon the adrenals is necessary for the development of the lesion.

The amount of exogenous ACTH required to produce the lesion in normal animals under the conditions of these experiments was very large, but reasons are given for believing that, under the conditions of fulminant infection the pituitary may produce an amount of adrenocorticotropic hormone sufficient to cause the lesion.

Other effects of ACTH upon the adrenal cortical cells in these experiments are discussed.

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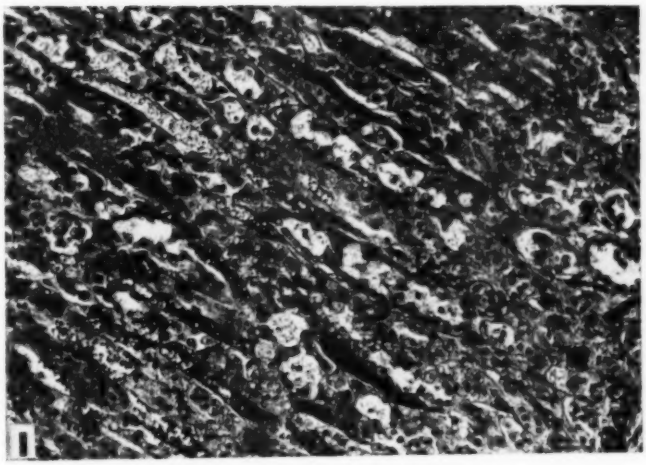
## EXPLANATION OF ILLUSTRATIONS

(Photographs by Mrs. Joan Bailey)

FIG. 1. Tubule formation in adrenal cortex of patient dying of meningococcal meningitis with circulatory collapse (Autopsy 18,205). Some of the tubules contain a few polymorphonuclear leucocytes.

FIG. 2. Tubule formation in adrenal cortex of rat 45R, resulting from treatment with ACTH (See Table I). There are polymorphonuclear leucocytes in several tubules at the upper right.



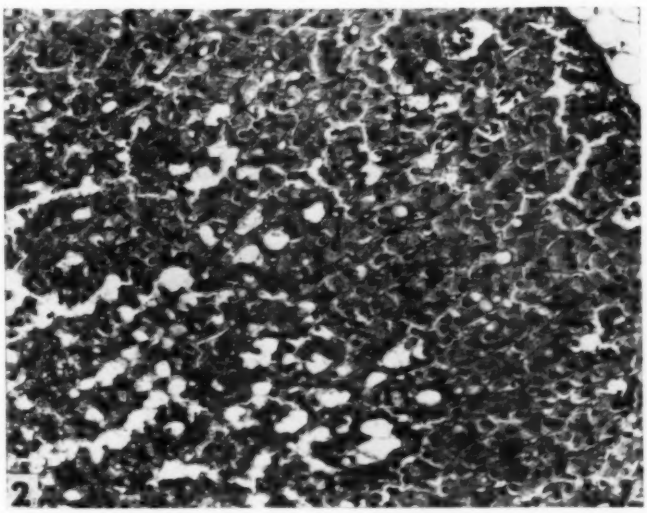
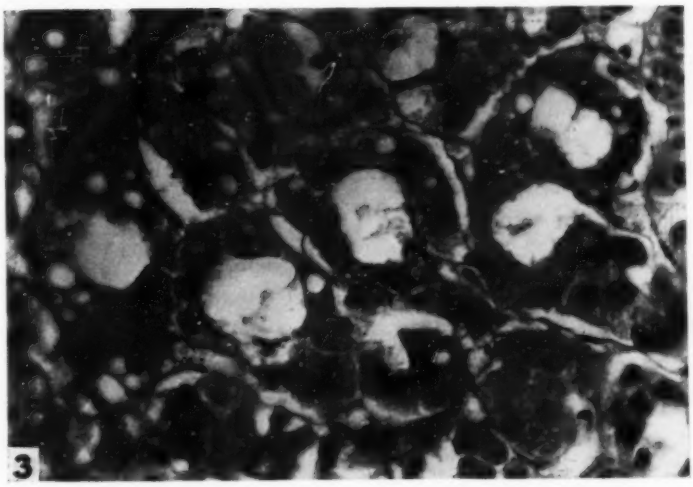


FIG. 3. Tubules in adrenal cortex of patient dying of suppurative nephritis (Autopsy 24,030). A dead cortical cell in a tubule at top and in one at lower right corner.

FIG. 4. Tubules in adrenal cortex of rat 45R, resulting from treatment with ACTH (See Table I). Dead cortical cells in several tubules. Compare with Fig. 3.



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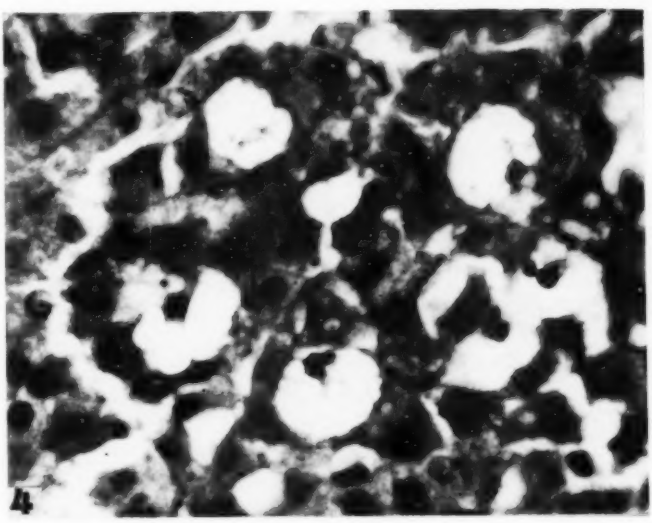

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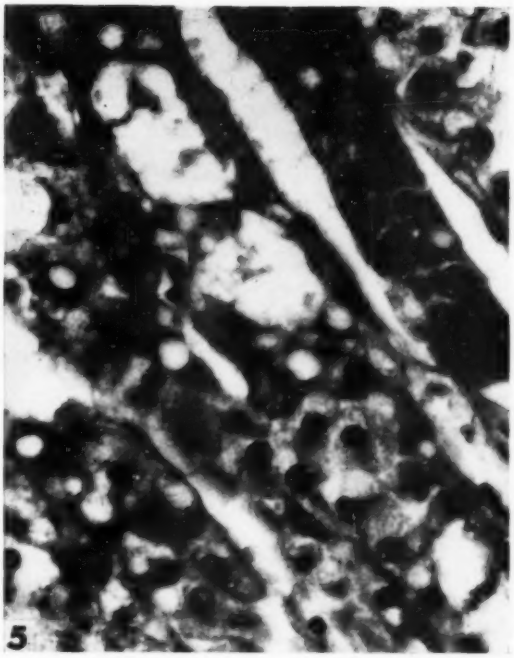
FIG. 5. Tubule formation in human adrenal cortex (same patient as Fig. 3).

FIG. 6. Tubule formation in adrenal cortex of rat 45R, resulting from treatment with ACTH (See Table I). Compare with Fig. 5.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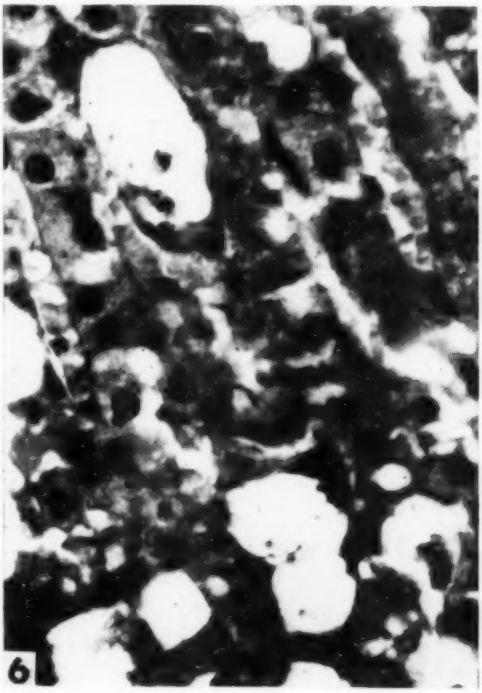
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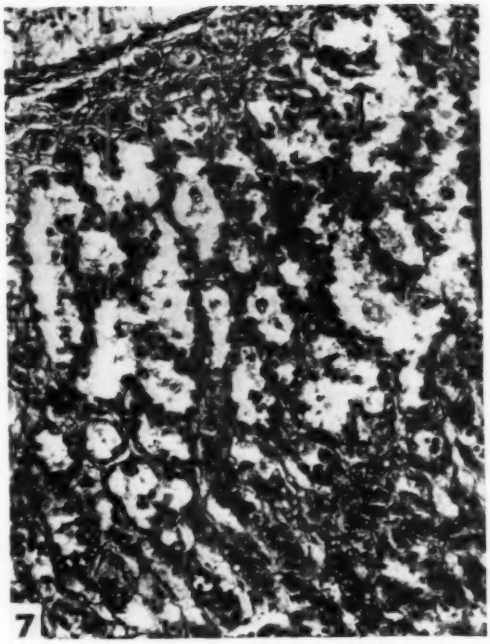
FIG. 7. Extreme tubular degeneration of adrenal cortex of patient dying of meningococcal meningitis with circulatory collapse (Autopsy 18,205). The remaining cortical cells that border the capillary network have lost most of their cytoplasm. There is protein-containing fluid in the spaces between the widely separated cell strands.

FIG. 8. Extreme tubular degeneration of adrenal cortex of rat 77S, resulting from treatment with ACTH (See Table I). Compare with Fig. 7.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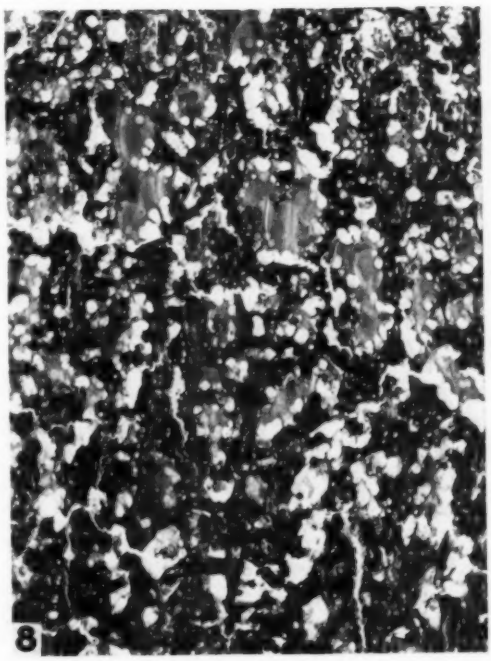
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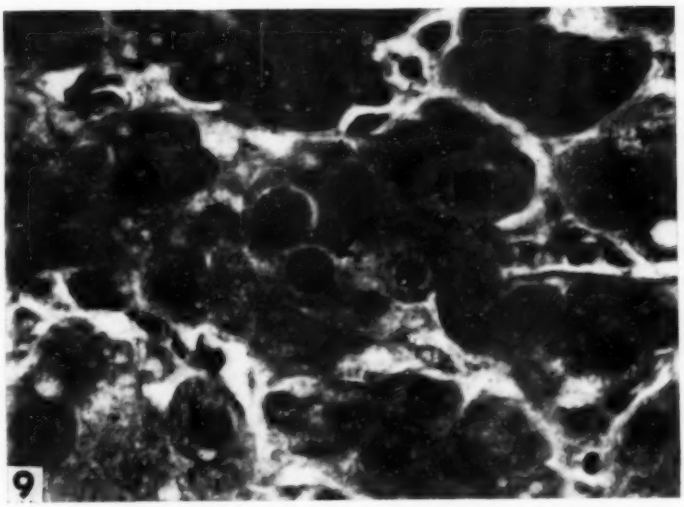
FIG. 9. Colloid globules in cells of zona fasciculata of adrenal cortex of patient dying of streptococcal meningitis (Autopsy 24,079).

FIG. 10. Colloid globules in cells of zona fasciculata of adrenal cortex of rat 2P, resulting from treatment with ACTH (See Table I). Compare with Fig. 9.



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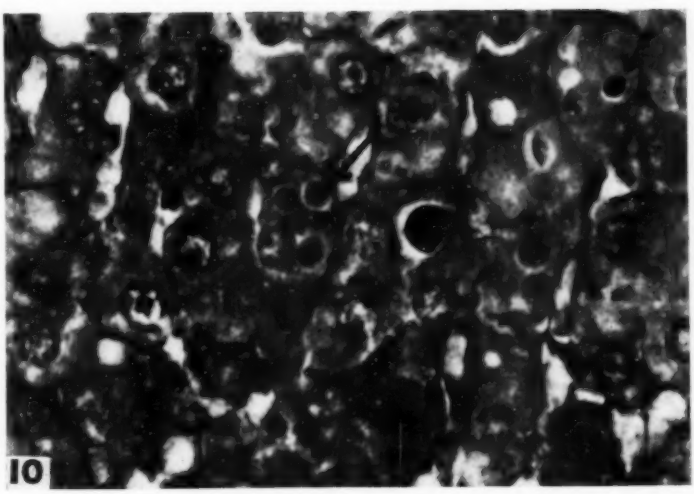

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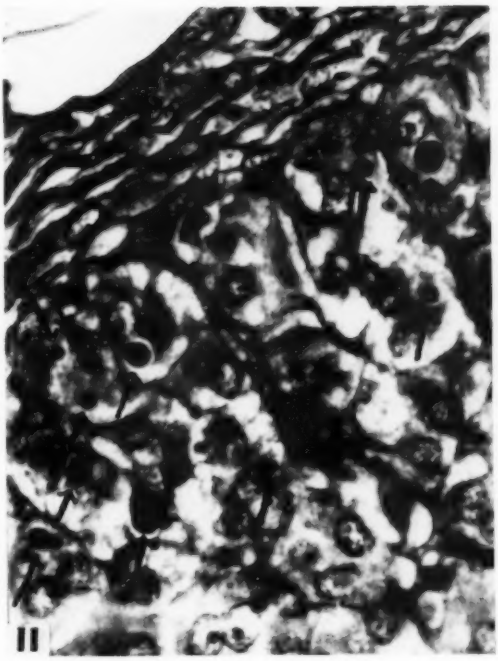
FIGS. 11 and 12. Colloid globules in cells of zona glomerulosa of adrenal cortex of rat 2P, resulting from treatment with ACTH (See Table I).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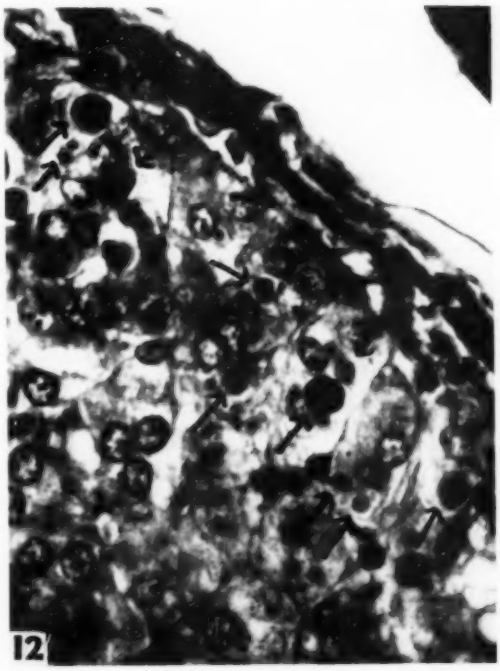
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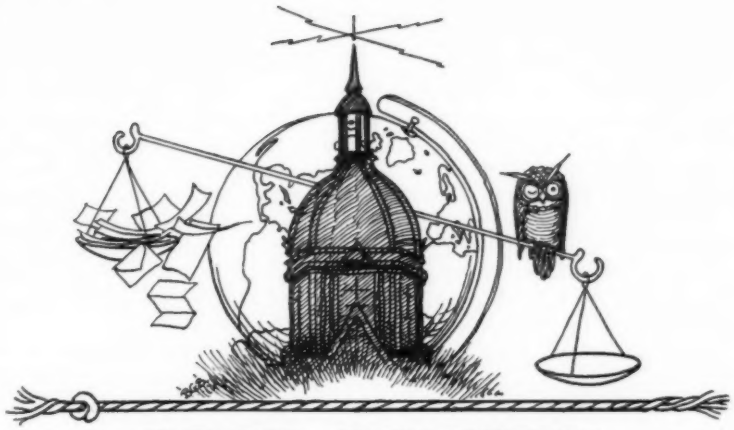

# BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

**Psychiatry and Medical Education.** Report of the 1951 Conference on Psychiatric Education held at Cornell University, Ithaca, New York, June 21–27, 1951. Organized and conducted by the American Psychiatric Association and the Association of American Medical Colleges. 164 pp., $1.00. American Psychiatric Association, Washington, D. C.

This publication is the report of the Conference on Psychiatric Education which was organized and conducted by the American Psychiatric Association and the Association of American Medical Colleges, and held at Cornell University, Ithaca, New York, June 21–27, 1951.

The report was prepared by an editorial board consisting of Drs. John C. Whitehorn, Chairman, Carlyle Jacobsen, Maurice Levine and Vernon W. Lippard. The Board has editorial assistants Stella Bloch Hanan and Robert L. Robinson.

The scope of the Conference was limited to a consideration of psychiatry in relation to undergraduate medical education, hence the report deals with that subject only.

The report itself is divided into eight chapters and there are three appendices containing factual information in reference to the conference.

It is an excellent document and well worth reading by all who are interested in medical education as a whole, as well as by those who are concerned only with the psychiatric aspects of medical education.

Unlike most reports of such conferences, this document has a unity of style which makes for easy reading and throughout there are many references which should prove useful to anyone who wishes more information in reference to particular topics. All in all the report is an excellent document of its kind and the Editorial Board deserves much credit for an outstanding performance.

ALAN M. CHESNEY

**Surgical Technique.** By STEPHEN POWER. 380 pp., $6.50. J. B. Lippincott Co., Philadelphia, Pa.

This little volume by an English surgeon has the important virtue of being light enough to hold in the hand. It is further unusual among surgical texts in being written with a light-

ness of style and an absence of stuffiness that distinguishes English scientific writers. It is far more than a rehash of previous publications. It is a distillate of the experience and wisdom of a surgeon who has learned by careful observation, and by maintaining a thoughtful attitude towards the classical rules of surgery. The simple line drawings transmit principles better than more elaborate illustrations frequently do. The book is worthwhile reading for the house surgeon. It should be entertaining and provocative for the mature surgeon as well.

WILLIAM E. GROSE

**Physical Examination of The Surgical Patient.** By J. ENGLEBERT DUNPHY AND THOMAS W. BOTSFORD. 326 pp., $7.50. W. B. Saunders Co., Philadelphia, Pa.

This book champions a return to more careful examination of the surgical patient in these days when the trend is to look more and more toward special studies and less and less at the patient. It is directed primarily at the young surgeon or medical student but contains helpful information for all. Certain sections are particularly good, namely those related to the breast, peripheral vessels, and to the abdomen (which is divided into elective examination of the acute and post operative abdomen, and the abdomen of infants and children). A large portion of the book related to the emergency examination is especially helpful.

Several minor omissions might be noted, such as percussion of the abdomen with the patient on his hands and knees to detect small amounts of free fluid, or the significance of unilobar hepatic enlargement and large bosses in carcinoma as contrasted with the usual more general enlargement and fine irregularity in cirrhosis. In general the book is distinguished more by careful description of certain techniques of evaluation than by listing small tricks of the trade which often allow masters of the art to make accurate diagnoses from one or two physical signs.

For better of for worse, eponyms are avoided almost as if the authors passionately disliked them. The well known sign of pain in the calf on dorsiflexion of the foot in the patient with phlebitis is no more specifically labelled, although the book is dedicated to Drs. Homans and Cheever.

Students, surgeons and internists will find this a welcome supplement, though not a substitute, for the several books available on general physical examination.

HENRY T. BAHNSON

**Liver Injury.** Transactions of the 11th Conference, April 30 and May 1, 1953. Edited by F. W. HOFFBAUER. 265 pp., $4.00. The Josiah Macy, Jr. Foundation, New York.

The latest volume of the conferences of liver injury covers the usual gamut of subjects, informally discussed by a group of experts. Of particular interest to this reviewer is the summary by Dr. Mirick of the work which he and Janet Jordan carried out on infectious hepatitis in mice. Dr. Mirick stressed their belief that this disease is not identical with human infectious hepatitis. Dr. Joseph Stokes described the experience of his group and that of Dr. Capps in the epidemiology of hepatitis in an orphanage, data which have since been published elsewhere. Dr. John Waterlow, of the University College of the West Indies, spoke about his micro-techniques for the study of the enzymic activity of sections of liver removed by punch biopsy. This is certainly a fundamental approach to the problems of hepatic disease, but those of us who have witnessed some of the untoward effects of punch biopsy may have some reservations concerning the use of this technique. There is an extensive chapter by Dr. Max Elias of the Chicago Medical School concerning his revolutionary views about the morphology of the liver lobule, namely, that the cells of the liver are not arranged in cords but in plates. "While we formerly believed in cylinders of liver cells,

surrounded by blood, we see now that the liver consists of cylinders of blood surrounded by liver cells." Although this discussion is profusely and beautifully illustrated, the concept is a difficult one which may need clarification.

In previous reviews, the difficulties imposed upon the reader searching for information rather than entertainment have been stressed. This set of Transactions, alas, is no different. It is amusing to note that we now have not only a copy of the script of the play, but also a section of nine pages listing the *dramatis personae*. Those acidulously inclined may wonder whether Samuel French will publish the next volume. As always, the Transactions educate and amuse, but a more formal arrangement of the text, and an index for each volume would be welcome.

OSCAR D. RATNOFF

**Aviation Toxicology.** By the Committee on Aviation Toxicology of the Aero Medical Association. Edited by C. R. SPEALMAN. 120 pp., $4.00. The Blakiston Co., New York.

This small compendium is valuable and well done. One penalty which our society pays for the headlong rush of its industrial and chemical development is that the profusion of potentially hazardous products to which men are exposed far exceeds the capacity of the toxicologists to screen them and to devise protective and therapeutic measures for them all. As a result safety measures must be developed largely on general principles having to do with the physiological hygiene of exposures and the familial characteristics of the chemical group to which the agent belongs. With such information at hand reasonably effective protection can be planned and accomplished, with some unpleasant exceptions which must be faced as a calculated risk. Dr. Spealman and his committee have made available a simple and clear exposition of these principles and have provided much general, and a reasonable amount of specific, information on many of the agents which are involved in aviation. It may be noted, however, that the list of compounds in present use, especially in advanced military design and use, contains a number of substances which do not appear in this text. this is, therefore, a handy and authoritative book which does not purport to be all-inclusive, but treats of general principles and of some specific areas with skill and sound knowledge.

JOSEPH L. LILIENTHAL, JR.

**The Roots of Psychotherapy.** By Carl A. Whitaker and Thomas P. Malone. 236 pp., $4.50. The Blakiston Co., New York.

Psychotherapy, an art involving the complex interplay of therapist and patient at both conscious and unconscious levels, is extremely difficult to conceptualize and describe. This book is a valiant effort by two experienced therapists to put into words a process which they conceive of as essentially intuitive and non-verbal. Inevitably they do not fully succeed, but they have produced an intensely interesting and provocative formulation.

Psychotherapy is conceived as grounded in the biological processes of maturation and adaptation. It is an attempt to catalyse intrapsychic growth and repair through a particular type of interpersonal relationship. Anything short of this, for example, increasing a patient's capacity to utilize his present assets more successfully, or modifying his environment so that he is more comfortable, is not considered to be real psychotherapy.

The ambitious aim of freeing the patient's energies for further growth is brought about through an experience characterized by intense emotional interplay between therapist and patient at an unconscious, symbolic, largely non-verbal level. This "core" experience can occur only if the therapeutic situation is "isolated" from real life concerns of both therapist and patient. It implies great freedom of activity on the part of the therapist, including falling asleep in the interview and reporting his dreams to the patient, taking the patient into his

lap, giving him a bottle, or spanking him. By the same token therapy makes great demands on the therapist's intuitive ability, and each successful therapeutic experience contributes to his own emotional growth.

This is the kind of book that stimulates the reader to carry on a running discussion with the authors. The reviewer found much to object to and much with which to concur. His major disagreement is with the emphasis on the exclusion of all real life considerations from the therapeutic situation. Though some isolation from concerns of everyday life is necessary, too great a gap may impede the carry-over of what is learned in therapy to daily living, which is the final test of therapeutic success.

On the other hand many points are very well taken, among them the insistence that the important therapeutic forces lie in the present relationship rather than the patient's past, and the view of therapy as a bilateral process, largely intuitive and emotional, in which the therapist's own needs and vulnerabilities, as well as his strength, play an important part and through which he too is modified.

This book is too abstract to be of much help to beginners—it cries aloud for more illustrative material. It is, however, heartily recommended to experienced psychotherapists who will find its thought-provoking formulations richly rewarding.

JEROME FRANK

**Mr. Tompkins Learns the Facts of Life,** By G. GAMOW. 88 pp., $2.75. Cambridge University Press, New York.

This new volume of the adventures of Mr. Tompkins is pure delight. Dr. Gamow is a physicist used to thinking in cosmic terms. Now he turns to the microcosm of human biology. His mouthpiece is Mr. Tompkins, the Professor's son-in-law. Mr. Tompkins is fortunate enough in his dreams to be able to travel around his own body learning about metabolism, immunity, neurophysiology and so forth in what one might call anthropomorphic terms. He learns about enzymes when a lipase attacks him while he is visiting the intestines. He is lectured to on heredity by a little old woman who turns out to be a kindly maternal gene. Maniac, the lightning electronic calculator teaches him about thought processes. I suppose one could quarrel about a few factual errors, but these seem of no importance. The lay reader will learn in simple terms about modern concepts of biochemistry and biophysics at a cellular and molecular level. Those who perhaps know some of the subject matter will wish that they had said it as well.

OSCAR D. RATNOFF

**Proceedings of the Forum Sessions:** Thirty-Eighth Clinical Congress of the American College of Surgeons, New York City, September, 1952. Surgical Forum Committee: OWEN H. WANGENSTEEN, Chairman, J. GARROTT ALLEN, WARREN H. COLE, ROBERT E. GROSS, CARL A. MOYER, I. S. RAVDIN AHD H. B. SHUMACKER. 716 pp., $10.00. W. B. Saunders Co., Philadelphia, Pa.

The Surgical Forum annually becomes more of an outstanding meeting of the year, and this bound volume of the papers presented becomes more a must for one anxious to keep abreast of surgical progress. The work of over 325 investigators, this collection contains many important physiological, chemical, and biophysical contributions on which future surgical practice will be based. The brief reports are grouped into sections for easy perusal by those interested in various branches of general, plastic, and vascular surgery, gynecology and obstetrics, and anesthesia.

For either browsing over short articles or more concentrated study this volume is highly recommended.

HENRY T. BAHNSON

## BOOKS RECEIVED FOR REVIEW

**Adrenal Cortex.** Transactions of the Fourth Conference Nov. 12, 13, 14, 1952, New York. Edited by ELAINE RALLI. 165 pp., $4.00. The Josiah Macy, Jr. Foundation, New York.

**Bacterial Genetics.** By WERNER BRAUN. 238 pp., $6.50. W. B. Saunders Co., Philadelphia, Pa.

**Die Bewegungsbestrahlung.** By F. WACHSMANN AND G. BARTH. 192 pp., Ganzleinen DM 36. Georg Thieme Verlag, Stuttgart, Germany.

**Die entschädigungspflichtigen Berufskrankheiten.** By M. BAUER. 176 pp., kartoniert DM 9.60. Georg Thieme Verlag, Stuttgart, Germany.

**Die Nahbestrahlung.** By HENRI CHAOUL AND FELIX WACHSMANN. 225 pp., Ganzleinen DM 39. Georg Thieme Verlag, Stuttgart, Germany.

**Die Teleröntgentherapie.** By W. TESCHENDORF. 72 pp., kartoniert DM 8.70. Georg Thieme Verlag, Stuttgart, Germany.

**Handbook of Differential Diagnosis.** By HAROLD THOMAS HYMAN. 716 pp., $6.75. J. B. Lippincott Co., Philadelphia, Pa.

**New and Nonofficial Remedies.** Issued Under the Direction and Supervision of The Council on Pharmacy and Chemistry of the American Medical Association for 1953. 623 pp., $2.65. J. B. Lippincott Co., Philadelphia, Pa.

**Operative Surgery,** 6th edition. Vols. I and II. By Guy W. Horsley and Isaac A. Bigger. 1579 pp. $30.00. The C. V. Mosby Co., St. Louis, Missouri.

**Pediatrics.** By L. EMMETT HOLT, JR. AND RUSTIN MCINTOSH. 1485 pp., $15.00. Appleton-Century-Crofts, Inc., New York.

**Risiko und Kosten in der Krankenpflegeversicheruing.** By ALFRED J. HOSCH. 127 pp., $2.80. A. Francke Ag. Verlag, Bern, Switzerland.

**Rudolf Virchow: Doctor, Statesman, Anthropologist.** By ERWIN H. ACKERKNECHT. 304 pp., $5.00. The University of Wisconsin Press, Madison, Wisconsin.

**Side Effects of Drugs.** By L. MEYLER. Translated by Ph. Viujsje and W. Mulhall Corbet. 268 pp., $5.50. Elsevier Publishing Co., Houston, Texas.

**Stedman's Medical Dictionary.** Edited by NORMAN BURKE TAYLOR in collaboration with ALLEN ELLSWORTH TAYLOR. 1561 pp., $11.50. The Williams & Wilkins Co., Baltimore, Md.

**Surgical Pathology.** By LAUREN V. ACKERMAN. 836 pp., $14.50. The C. V. Mosby Co., St. Louis, Missouri.

**The Team Plan: A Manual for Nursing Service Administrators.** By DOROTHY PERKINS NEWCOMB. 82 pp., $1.50. G. P. Putnam's Sons, New York.